

Current Clinical Strategies

Manual of HIV/AIDS Therapy

1997 Edition

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Epidemiology of HIV and AIDS

I. Epidemiologic Trends for HIV and AIDS in the United States

- A.** An estimated 1 million people in the United States are infected with HIV, and about half may be unaware of their condition. Approximately 40,000-80,000 new infections are diagnosed each year.
- B.** AIDS is the number one cause of death in persons 25-44 years old. It is the leading cause of death in men, and it is the third leading cause of death in women.
- C.** An estimated 55,000 residents of the United States die each year from HIV infection.
- D.** One in four new HIV infections occur in people younger than 20.
- E. Total AIDS Cases Through December 1995**
 - 1. Adults:** 506,000 cases; 316,000 deaths
 - 2. Children:** 6,900 cases; 3,900 deaths
- F. Epidemiologic Trends by Transmission Category**
 - 1.** In gay men there has been a plateau in the number of new cases since 1991.
 - 2.** In injecting drug users and heterosexual contacts there are continuing increases in new cases.
 - 3.** In gay men the greatest proportionate increase has been among black and Hispanic men, men from the South, and in men from small towns and rural areas.
 - 4.** In New York City, Los Angeles, and San Francisco, the number of cases has been decreasing in white men while increasing in black men.

II. Emerging Trends in Women

- A.** There has been a continuing increase in the incidence of AIDS attributed to heterosexual HIV transmission. Sexual contact is the leading mode of HIV acquisition in women.
- B.** There has been a disproportionate impact of AIDS on black and Hispanic women.
- C. Risk Factors for HIV Transmission in Non-IV Drug User Women**
 - 1.** Multiple sex partners
 - 2.** Exchange of sex for drugs or money
 - 3.** Syphilis

III. International Magnitude of the AIDS Epidemic

- A.** More than 4.5 million AIDS cases; >70 % of cases are from Africa
- B. HIV infection**
 - 1.** Cumulative total of 18 million HIV-infected adults and 1.5 million HIV-infected children.
 - 2.** More than half of all infected persons are from sub-Saharan Africa where the prevalence in urban child-bearing women is as high as 30%, and the prevalence in female prostitutes is as high as 85%
 - 3.** The most rapid increase in HIV prevalence is occurring in south and southeast Asia.

Care of the HIV-Infected Patient

Initial Evaluation of the HIV-Infected Patient

An estimated 1 million people in the United States are infected with HIV, and about half may be unaware of their condition. Approximately 40,000-80,000 new infections are diagnosed each year.

I. The HIV Testing Method

- A. The first step in diagnosis is an enzyme-linked immunosorbent assay (ELISA) to detect HIV antibodies.
- B. If the ELISA is positive, the result is confirmed with a Western blot test, which is much more specific. The HIV RNA test may replace the ELISA.
- C. There is a window period between infection with HIV and the development of antibody levels; within 6 months of infection, 95% of those infected have detectable antibody.

II. Initial Clinical Evaluation of the HIV-Infected Patient

- A. The presence of constitutional symptoms, particularly sustained fever, is strongly correlated with a poorer prognosis. Symptoms of opportunistic infections, weight loss, oral, gastrointestinal, pulmonary or dermatologic symptoms should be assessed.
- B. The history also includes hospital visits, operations, immunizations, drug allergies, infectious diseases, sexual and drug-use history, medications, blood and organ donation history, and social history.
- C. Explain the typical disease course, and verify that patients understand the risk they pose to others. Advice includes avoiding raw or undercooked meats (toxoplasmosis), uncooked shellfish (*Vibrio* species), cat feces (toxoplasmosis), and cat bites, licks, or scratches (*Bartonella*).
- D. **Physical Examination**
 1. **The overall assessment** should look for evidence of wasting and weight loss.
 2. **Oral Examination:** The oral cavity should be thoroughly examined for candidiasis and hairy leukoplakia.
 3. **Ophthalmologic Findings:** Retinal hemorrhages and exudates may indicate cytomegalovirus retinitis. The appearance resembles "ketchup and cottage cheese."
 4. **Lymph Nodes:** Generalized lymphadenopathy may be present.
 5. **Dermatological Findings:** Rashes, Kaposi's sarcoma (brown/purple plaques), seborrheic dermatitis, zoster, herpes, fungal and bacterial infections may be detected.
 6. **Neurologic Examination:** Confusion may indicate AIDS dementia complex. Motor deficits may indicate CNS toxoplasmosis or lymphoma. Decreased visual acuity and visual field deficits may indicate cytomegalovirus or toxoplasmosis.

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Initial Physical Exam of the HIV-infected Patient

Area	Finding	Possible Cause
General	Weight loss Fever	HIV wasting syndrome Consider Mycobacterium avium complex, TB or lymphoma if localizing signs of infection are absent
Fundusoscopic exam	Yellow-white retinal infiltrates Retinal hemorrhage	CMV or toxoplasma retinitis CMV retinitis, varicella-zoster virus retinitis
Visual-field exam	Field deficits	CMV or toxoplasma retinitis, syphilitic optic neuritis
Oral Cavity Exam	White plaques White lesions on lateral aspects of tongue Oral ulcers Violaceous macule or papule	Oral candidiasis Hairy leukoplakia HSV, CMV, or aphthous ulcers Kaposi's sarcoma
Lymph Nodes	Lymphadenopathy	AIDS-related lymphadenopathy, lymphoma, TB, syphilis
Abdominal	Hepatomegaly or splenomegaly Perirectal ulcer	Mycobacterium avium complex, TB, lymphoma, histoplasmosis HSV, CMV
Genital	Genital lesions	Syphilis, HSV, chancroid, condyloma acuminata, molluscum contagiosum
Neurologic	Motor deficits	CNS toxoplasmosis, lymphoma, neurosyphilis, TB, progressive multifocal leukoencephalopathy, peripheral neuropathy
Skin	Violaceous papule or macule Scaling lesions Papular eruption Purpura Vesicular rash	Kaposi's sarcoma, bacillary angiomatosis Seborrheic dermatitis, fungal infection, psoriasis Staphylococcal folliculitis, scabies, molluscum contagiosum, eosinophilic folliculitis AIDS-related idiopathic thrombocytopenic purpura Herpes zoster, HSV, drug reaction

III. Initial Baseline Laboratory Evaluation of HIV-Infected Patients

- A.** Complete blood cell count with differential and platelet counts; repeat with each CD4 count
1. Baseline liver and renal function tests, electrolyte panel
 2. Purified protein derivative (PPD) test (anergy testing is not necessary) interpreted within 48 to 72 hours
 3. Genital sexually transmitted disease testing for gonorrhea and chlamydia
 4. Hepatitis B screen (hepatitis B surface antigen, hepatitis B antibody)
 5. Toxoplasma IgG serology (identifies patients at risk)
 6. Chest X-ray
 7. VDRL or RPR (confirmed with a specific treponemal test)

B. Immune Function Testing

1. The CD4 count is a general indicator of the patients level of immune function.
2. Quantitative HIV RNA should also be measured, and it provides a more precise indicator of prognosis.

C. Initial Gynecologic Evaluation of HIV-Infected Women

1. A Pap smear should be completed and repeated every 6 months. If two are sequentially normal, repeat annually.
2. Women of childbearing age need counseling on reproductive options and contraception.

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Initial Care of HIV-Infected Adults

I. First Visit

A. Full history and Assessment of Symptomatic Complaints

B. Patient Education and Counseling

1. Explain stages of HIV infection and uncertain prognosis.
2. Describe preventive strategy and stress the importance of early detection of illnesses and infections.
3. Review sexual and drug-use behaviors, and safer sex practices, advise against sharing of needles, and advise use of bleach to sterilize needles.
4. Discuss woman's reproductive and contraceptive options.
5. Identify sexual and intravenous drug-use contacts for contact notification.
6. Address lifestyle issues: Diet, exercise, avoidance of unhealthy habits.

C. Immunizations

1. Polyvalent pneumococcal polysaccharide vaccine
2. Hepatitis B vaccine

D. Complete Physical Examination: Special attention to skin lesions, oral cavity, lymphadenopathy, genitourinary and rectal evaluation, gynecologic examination and Pap smear; and neurologic assessment including mental status

E. Laboratory Tests

1. CBC
2. Baseline chest film
3. Hepatitis B screen (surface and core antibodies)
4. Tuberculin purified protein derivative (PPD)
5. CD4 cell profile
6. HIV RNA
7. Toxoplasma titer
8. VDRL
9. Serum chemistry panel

F. Referral to Support Systems: Support groups, psychologist

II. Second and Subsequent Visit (1-2 weeks later)

A. Inquire about problems since last visit and evaluate

B. Review laboratory results from first visit

C. If PPD Test was positive, initiate isoniazid prophylaxis; if patient has history of exposure, initiate isoniazid prophylaxis, regardless of PPD result.

D. Follow-up Laboratory Data

1. CD4 Count

- a. If <500 cells/ μ L, recommend antiretroviral therapy
- b. If <200 cells/ μ L, initiate *Pneumocystis carinii* pneumonia prophylaxis
- c. If <100 cells/ μ L, start toxoplasmosis prophylaxis and consider *Mycobacterium avium* complex prophylaxis
- d. If <50 cells/ μ L, do screening ophthalmologic examination

2. VDRL: If positive and history suggestive of untreated disease, assess carefully for signs of neurosyphilis and do a lumbar puncture and treat as needed

3. Hepatitis B: If no evidence of prior exposure and potentially at risk, give vaccination

IV. Centers for Disease Control HIV Classification System

A. Category A refers to Asymptomatic HIV infection, acute (primary) HIV illness, and asymptomatic persistent generalized lymphadenopathy.

B. Category B includes symptomatic conditions that are not included in

category A or C. Examples include but are not limited to:

1. Bacillary angiomatosis
2. Candidiasis, vulvovaginal: Persistent >1 month, poorly responsive to treatment
3. Candidiasis, oropharyngeal
4. Cervical dysplasia, severe, or carcinoma in situ
5. Constitutional symptoms such as fever (38.5 C) or diarrhea >1 month

C. AIDS (Category C): Any HIV-infected patient with **less than 200 CD4 cells/ μ L** is diagnosed with AIDS, and any patient who contracts an **opportunistic infection** is diagnosed with AIDS regardless of CD4 count.

D. Opportunistic AIDS-Defining Illnesses

- | | |
|--|---|
| 1. Pneumocystis carinii pneumonia | duration; or causing bronchitis, pneumonia, or esophagitis |
| 2. Pneumonias, recurrent (2 or more episodes in 1 year) | 12. Histoplasmosis (disseminated) |
| 3. Candidiasis: Esophageal, tracheal, bronchial | 13. Isosporiasis, with diarrhea lasting >1 month |
| 4. Kaposi's sarcoma | 14. Non-Hodgkin Lymphoma: Burkitt's, immunoblastic sarcoma, or primary CNS lymphoma |
| 5. Cervical cancer, invasive | 15. M. avium or M. kansasii, extrapulmonary |
| 6. Coccidioidomycosis, extrapulmonary | 16. M. tuberculosis, pulmonary or extrapulmonary |
| 7. Cryptococcosis, extrapulmonary | 17. Progressive multifocal leukoencephalopathy |
| 8. Cryptosporidiosis, chronic intestinal, with diarrhea lasting >1 month | 18. Salmonella bacteremia, recurrent |
| 9. Cytomegalovirus retinitis or disease of other than liver, spleen, lymph nodes | 19. Toxoplasmosis, cerebral |
| 10. HIV encephalopathy (AIDS dementia complex) | 20. Wasting syndrome due to HIV |
| 11. Herpes simplex with mucocutaneous ulcer >1 month | |

V. Vaccination

- A.** Pneumococcal polysaccharide vaccine should be given unless the patient has been immunized.
- B.** Hepatitis B vaccine is suggested for HIV positive patients with no evidence of immunity to hepatitis B (HBs-antibody negative) who continue to engage in risk behavior.

VI. Antiretroviral Therapy

- A.** Antiretroviral therapy is recommended in patients with CD4⁺ cell counts below 500 cells/ μ L.
- B. Asymptomatic patients with CD4⁺ cell counts above 500 cells/ μ L:**
 1. Antiretroviral therapy is recommended for those with more than 30,000 to 50,000 HIV RNA copies/ μ L or with rapidly declining CD4⁺ cell counts (ie, a greater than 300 cells/ μ L loss over 12 months).
- C. Symptomatic Patients:** Antiretroviral therapy should be initiated in all patients with symptomatic HIV disease (eg, recurrent mucosal candidiasis; oral hairy leukoplakia; chronic or otherwise unexplained fever, night sweats, or weight loss).
- D.** See "Antiretroviral Therapy," page 19

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VII. Prophylaxis Against Opportunistic Infections

- A. Prophylaxis against *P. carinii* pneumonia has been shown to reduce the incidence of this complication. It is indicated for patients with either a CD4 count under 200/ μ L, previous *P. carinii* pneumonia, or persistent thrush or unexplained fevers regardless of CD4 count.
 - 1. Prophylactic treatment to prevent PCP consists of one double-strength trimethoprim/sulfamethoxazole tablet daily or three times a week.
 - 2. Also see "Pneumocystis carinii Pneumonia," page 97
- B. **Toxoplasmosis Prophylaxis:** Primary prophylaxis is indicated for patients with positive antibodies for toxoplasmosis when the CD4 cell count is <100/ μ L. TMP/SMX and dapsone are both active against PCP, and also provide prophylaxis against toxoplasmosis.
- C. **Mycobacterium Avium Complex Prophylaxis** has been approved for HIV-infected patients with CD4 counts <100/ μ L.
 - 1. The frequency of MAC can be moderately reduced by prophylaxis using either or clarithromycin (500 mg bid) or rifabutin (Mycobutin) (150 mg bid or 300 mg qd).
 - 2. Also see "Mycobacterium Avium Complex," page 95.

VIII. Pretest Counseling Before HIV Testing

- A. **Determine the reason for testing and Evaluate Basic Health Status.** Look for symptoms of HIV infection.
- B. **Assess Risk Factors for HIV Infection**, including number and sex of partners, condom use, HIV risk of partners, and drug use (intravenous drugs).
- C. **Explain the Test:** Discuss the possibility of a false-negative result if infection was recent. Inform the patient that the asymptomatic period from infection to AIDS is often 11 years. Assess the suicide risk.
- D. **Obtain informed consent for the test.**

IX. Posttest Counseling After HIV Testing

- A. **Assess the patient** for the potential for suicide or violence.
- B. **Clarify the meaning of the test result:** If the test is negative and the patient has engaged in risk behaviors during the past 3 months, recommend retesting in 2-3-months. Reinforce risk-reduction.
- C. **Explain that infection can be transmitted** to others through unsafe sex, shared needles, blood donation, and contact with infected blood. Encourage condom use and cessation of IV drugs, or use of needle exchange programs or bleach to clean needles. Explain that common household contact does not transmit HIV.
- D. **Provide a Medical Follow-up Plan** and Arrange for Contact Notification.
- E. **Provide telephone numbers** for an AIDS hot line and other support groups and services.

References: See page 108.

Primary Care of the HIV-Infected Patient

I. Ongoing Primary Care of the HIV-Infected Patient

- A. Ongoing primary care includes treatment of acute infections, monitoring of physical and mental status, tracking the CD4 cell count and HIV RNA, and assurance that the patient is using appropriate prophylactic regimens and antiretroviral therapy.
- B. The CD4 cell count and HIV RNA value should be reviewed at each office visit. Infections will develop in most patients when the count drops below 200 cells/ μ L.
- C. The threshold for *Pneumocystis carinii* pneumonia is usually a CD4 level of around 200/ μ L. This is followed by toxoplasmosis encephalitis that usually develops at a CD4 level of about 100 cells/ μ L. Cytomegalovirus diseases (retinitis and enteritis) may reactivate beginning at CD4 levels of 100 cells/ μ L. Cryptococcal disease (typically meningitis) and *Mycobacterium avium* complex are seen at CD4 counts below 75 cells/ μ L.
- D. Once the CD4 count falls below 200 cells/ μ L or an opportunistic infection appears, the patient's diminished immune function warrants a diagnosis of AIDS.
- E. In females, a Papanicolaou smear should be obtained and repeated every 6 months. If two are sequentially normal, smears are repeated annually.
- F. CMV disease affects up to 45% of AIDS patients, and the vast majority (85%) of it is CMV retinitis. When the count drops to 100 cells/ μ L, ophthalmologic examinations should be performed every 6-12 months.

II. Frequency of Interventions

Intervention	Frequency
Physical examination	Every 6 months
Pap smear	Every 6 months
HIV RNA and CD4 cell count	Every 6 months ($>300/\mu$ L) Every 3 months (50-300/ μ L)
CBC	Every 6 months
Purified protein derivative	Yearly
VDRL (syphilis); serum chemistry panel	Yearly
Toxoplasmosis titer	Once at baseline if CD4 cell count $>100/\mu$ L; yearly until positive if CD4 cell count $<100/\mu$ L
Influenza virus vaccine	Every autumn
Pneumococcal vaccine	Initially

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III. Initiating Antiretroviral Therapy

A. When to Initiate Therapy

1. **Patients with CD4⁺ cell counts below 500 cells/ μ L:** Initiation of therapy is recommended in these patients.
2. **Asymptomatic patients with CD4⁺ cell counts above 500 cells/ μ L**
 - a. Treatment should usually be initiated for patients with HIV RNA levels higher than 5,000 to 10,000 copies/mL.
 - b. Treatment should usually be initiated if CD4⁺ cell counts are rapidly declining (ie, a greater than 300 cells/ μ L loss over 12-18 months).
3. **Symptomatic Patients:** Antiretroviral therapy should be initiated in all patients with symptomatic HIV disease (eg, recurrent mucosal candidiasis; oral hairy leukoplakia; chronic or otherwise unexplained fever, night sweats, or weight loss).

When to Initiate Treatment

CD4 cell Count (cells/ μ L)	Viral Load (RNA copies/mL)	Anti-HIV Treatment
>500 and Asymptomatic*	<5,000-10,000	Observation
>500 or Symptomatic*	>5,000-10,000	Monotherapy with didanosine (ddl) or stavudine (d4T) or 2 reverse transcriptase inhibitors (AZT + 3TC)
350-500 or Symptomatic*	<5,000-10,000	2 reverse transcriptase inhibitors (AZT + 3TC) or monotherapy with didanosine (ddl) or stavudine (d4T)
350-500	>5,000-10,000	2 reverse transcriptase inhibitors (AZT + 3TC). Add a protease inhibitor (indinavir) if needed to reduce viral load to <10,000 copies/mL
<350	any level	2 reverse transcriptase inhibitors (AZT + 3TC) plus a protease inhibitor (indinavir)

*Symptomatic HIV disease includes recurrent mucosal candidiasis, oral hairy leukoplakia, and chronic and unexplained fever, night sweats, and weight loss.

B. Initial Therapy Regimens

1. Zidovudine (AZT) 200 mg po tid/lamivudine (3TC) 150 mg po bid; a protease inhibitor may be added, such as indinavir (Crixivan) 800 mg tid
2. Zidovudine (AZT) 200 mg po tid/didanosine (ddl) 200 mg bid; a protease inhibitor may be added, such as indinavir (Crixivan) 800 mg tid
3. Zidovudine (AZT) 200 mg po tid/zalcitabine (ddC) 0.75 mg tid; a protease inhibitor may be added, such as indinavir (Crixivan) 800 mg tid
4. Didanosine (ddl) monotherapy 200 mg bid. Didanosine

monotherapy may be less effective as initial therapy in patients with more advanced human immunodeficiency virus (HIV) disease.

IV. Prophylaxis Against Opportunistic Infections

A. *Pneumocystis Carinii* Pneumonia Prophylaxis

1. Prophylaxis against *Pneumocystis carinii* pneumonia has been shown to reduce the incidence of this complication. It is indicated for patients with a CD4 count under 200/ μ L, previous *P. carinii* pneumonia, or persistent thrush or unexplained fevers regardless of CD4 count. If the CD4 count rises to above 200 after initiation of prophylaxis against PCP, prophylactic therapy should still be continued.
2. Prophylactic treatment to prevent PCP consists of one double-strength trimethoprim/sulfamethoxazole tablet daily or three times a week. Fever, drug rash and nausea frequently occur 9-12 days after the initiation of prophylaxis, and when symptoms are mild, they usually will pass.
3. Dapsone (100 mg/d) or aerosolized pentamidine (300 mg every four weeks) are acceptable alternatives for prophylaxis, though less effective, for patients who cannot take TMP/SMX.
4. Also see "*Pneumocystis carinii* Pneumonia," page 97

B. Toxoplasmosis Prophylaxis: Primary prophylaxis is indicated for patients with positive antibodies to toxoplasmosis when the CD4 count drops below 100 cells/ μ L. TMP/SMX and dapsone are both active against PCP and also provide prophylaxis against toxoplasmosis.

C. *Mycobacterium Avium* Complex Prophylaxis has been approved for HIV-infected patients with CD4 counts <100/ μ L.

1. Prophylaxis consists of clarithromycin (Biaxin) (500 mg bid), or azithromycin (Zithromax) 500 mg three times a week, or rifabutin (Mycobutin) (150 mg bid).

V. Complications of HIV Disease at Various CD4 Cell Counts

CD4 cell count	Condition
>500/ μ L	Acute retroviral syndrome * Candida vaginitis Persistent generalized lymphadenopathy
200-500/ μ L	Pneumococcal and other bacterial pneumonias* Tuberculosis (pulmonary)* Herpes zoster* Thrush Candida esophagitis Cryptosporidiosis (self-limited) B-cell lymphoma

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<200/ μ L	Pneumocystis carinii pneumonia* Disseminated chronic herpes simplex infection* Toxoplasmosis* Cryptococcosis* Disseminated histoplasmosis and coccidioidomycosis* Cryptosporidiosis (chronic) Microsporidiosis Tuberculosis (miliary/extrapulmonary)*
<50/ μ L	Disseminated cytomegalovirus infection* Disseminated Mycobacterium avium complex*

*Diseases that may present with fever

VI. Common Opportunistic Pathogens Causing Disease in HIV-Infected Patients

Pathogen	Usual Clinical Manifestations
Bacteria Haemophilus influenzae Salmonella species Shigella species Staphylococcus aureus Streptococcus pneumoniae	Pneumonia Enteritis, bacteremia Enteritis, bacteremia Soft-tissue disease, bacteremia Pneumonia, bacteremia
Candida albicans	Mucocutaneous disease, esophagitis
Cryptococcus neoformans	Meningitis
Cryptosporidium species	Enterocolitis
Cytomegalovirus	Retinitis, colitis, esophagitis
Herpes simplex virus	Mucocutaneous ulcers, esophagitis
Histoplasma capsulatum	Disseminated disease, pneumonia
Mycobacterium avium complex	Disseminated disease
Mycobacterium tuberculosis	Pneumonia, extrapulmonary disease
Pneumocystis carinii	Pneumonia
Toxoplasma gondii	Encephalitis
Treponema pallidum	Primary, secondary, and tertiary syphilis
Varicella-zoster virus	Cutaneous zoster, chicken pox

VII. Summary of Regimens for Acute Symptoms occurring in Patients with HIV Infection

Respiratory Infections	
Pneumocystis carinii pneumonia (21-d course in all instances)	Trimethoprim/sulfamethoxazole (Bactrim, Septra), 15 mg/kg/d of trimethoprim po or IV in three divided doses Pentamidine isethionate (Pentam 300), 3-4 mg/kg/d IV Dapsone, 100 mg/d po, plus either trimethoprim, 15 mg/kg/d po in 3-4 doses or pyrimethamine, 50-75 mg po qd
Disseminated	
Mycobacterium avium complex	Ethambutol HCl (Myambutol), 15-25 mg/kg/d po for at least 12 wk Clarithromycin (Biaxin), 500 mg po bid or azithromycin (Zithromax), 500 mg/d po Can add if no response: Rifabutin (Mycobutin), 300 mg/d po
Systemic Fungal Infections	
Coccidioidomycosis	Amphotericin B, 1.0 mg/kg/d IV Fluconazole (Diflucan), 400 mg po qd
Histoplasmosis	Amphotericin B, 1.0 mg/kg/d IV Itraconazole (Sporanox), 200 mg po bid
Oral and Esophageal Candidiasis (1-2 wk course in all instances)	
Oropharyngeal lesions	Fluconazole, 100-200 mg/d po Nystatin (Mycostatin, Nilstat), one 500,000-U tablet q6h Clotrimazole troches (Mycelex Troches), 10 mg 5 times/d Ketoconazole (Nizoral), 400 mg/d po
Esophageal lesions	Fluconazole, 200-400 mg po qd for 14-21 d Ketoconazole, 200 mg po bid for 14-21 d

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Gastrointestinal	
Diarrhea	Treat according to the underlying pathogen, otherwise Loperamide (Imodium), 4 mg po to start, then 2 mg q6h Diphenoxylate/atropine sulfate (Lomotil), 2.5-5.0 mg po 3-6 times/d for 24-48 h, then 2.5-5.0 mg tid and pm
Nausea and vomiting	Prochlorperazine (Compazine), 2.5-10 mg IV or 5-10 mg po or IM q6h or 25 mg per rectum q12h Metoclopramide HCl (Reglan), 10 mg po qid
Cryptosporidiosis	Paromomycin sulfate (Humatin), 750 mg po tid for 10-14 d or longer as needed
Dermatologic Conditions	
Seborrheic dermatitis	Hydrocortisone cream (2.5% for acute cases, 1% for maintenance treatment) plus ketoconazole cream 2% bid
Disseminated or persistent herpes simplex	Acyclovir, 5.0 mg/kg/dose IV q8h for 7-14 d (acute), 200-400 mg po 2-3 times/d
Herpes zoster	Acyclovir, 800 mg po 5 times/d for 7-10 d Famciclovir (Famvir), 500 mg po q8h for 7-10 days
Bacillary angiomatosis	Erythromycin, 500 mg po qid for 2 mo
Retinitis	
Cytomegalovirus (CMV) retinitis (induction)	Ganciclovir sodium (Cytovene), 5.0 mg/kg IV q12h for 14-21 d Foscarnet sodium (Foscavir), 90 mg/kg/dose IV q12h for 14 d
CMV retinitis (maintenance)	Ganciclovir, 5.0 mg/kg IV as 1-h infusion 7 times/wk or 6.0 mg/kg IV 5 times/wk.
Pain	
Peripheral neuropathy	Amitriptyline HCl (Elavil) or desipramine HCl (Norpramin), 25-150 mg po qhs Carbamazepine (Tegretol), 100-300 mg po bid

References: See page 108.

Antiretroviral Therapy

I. Initiating Antiretroviral Therapy

A. When to Initiate Therapy

1. Therapy of HIV infection should be initiated before irreversible immunologic damage has occurred.
2. **Patients with CD4⁺ cell counts below 500 cells/ μ L:** Initiation of therapy is recommended in these patients.
3. **Asymptomatic patients with CD4⁺ cell counts above 500 cells/ μ L**
 - a. Treatment should be initiated for patients with HIV RNA levels higher than 5,000 to 10,000 copies/mL, or observe.
 - b. Treatment should be initiated if CD4⁺ cell counts are rapidly declining (ie, a greater than 300 cells/ μ L loss over 12-18 months), or observe.
4. **Symptomatic Patients:** Antiretroviral therapy should be initiated in all patients with symptomatic HIV disease (eg, recurrent mucosal candidiasis, oral hairy leukoplakia, chronic or otherwise unexplained fever, night sweats, or weight loss).

When to Initiate Treatment

CD4 cell Count (cells/ μ L)	Viral Load (RNA copies/mL)	Anti-HIV Treatment
>500 and Asymptomatic*	<5,000-10,000	Observation
>500 or Symptomatic*	>5,000-10,000	Monotherapy with didanosine (ddl) or stavudine (d4T) or 2 reverse transcriptase inhibitors (AZT + 3TC)
350-500 or Symptomatic*	<5,000-10,000	2 reverse transcriptase inhibitors (AZT + 3TC) or monotherapy with didanosine (ddl) or stavudine (d4T)
350-500	>5,000-10,000	2 reverse transcriptase inhibitors (AZT + 3TC). Add a protease inhibitor (indinavir) if needed to reduce viral load to <10,000 copies/mL
<350	any level	2 reverse transcriptase inhibitors (AZT + 3TC) plus a protease inhibitor (indinavir)
*Symptomatic human immunodeficiency virus (HIV) disease includes recurrent mucosal candidiasis, oral hairy leukoplakia, and chronic and unexplained fever, night sweats, and weight loss.		

B. Initial Therapy Regimens

1. Zidovudine (AZT) 200 mg po tid/lamivudine (3TC) 150 mg po bid; a protease inhibitor may be added, such as indinavir (Crixivan) 800 mg tid

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2. Zidovudine (AZT) 200 mg po tid/didanosine (ddl) 200 mg bid; a protease inhibitor may be added, such as indinavir (Crixivan) 800 mg tid
3. Zidovudine (AZT) 200 mg po tid/zalcitabine (ddC) 0.75 mg tid; a protease inhibitor may be added, such as indinavir (Crixivan) 800 mg tid
4. Didanosine (ddl) monotherapy 200 mg bid. Didanosine monotherapy may be less effective as initial therapy in patients with more advanced human immunodeficiency virus (HIV) disease.

Antiretroviral Drugs

Drug	Usual Adult Dosage	Dosage Forms	Major Adverse Effects
Nucleoside analogs			
Zidovudine (Retrovir, AZT, ZDV)	200 mg three times daily	100-mg capsules	Anemia, headaches, nausea, myositis
Lamivudine (Epivir, 3TC)	150 mg twice daily	150-mg tablets	Nausea, headache
Didanosine (Videx, ddl)	200 mg twice daily	25-mg, 50-mg, 100-mg, 150-mg chewable tablets	Pancreatitis, diarrhea, peripheral neuropathy
Stavudine (Zerit, D4T)	20 mg twice daily	15-mg, 20-mg, 30-mg, 40-mg capsules	Peripheral neuropathy
Zalcitabine (Hivid, ddC)	0.75 mg three times daily	0.375-mg, 0.75-mg tablets	Oral ulcers, peripheral neuropathy, pancreatitis
Protease inhibitors			
Indinavir (Crixivan)	800 mg every 8 hours	200-mg, 400-mg capsules	Nephrolithiasis, Hyperbilirubinemia
Saquinavir (Invirase)	600 mg three times daily	200-mg capsule	Gastrointestinal disturbances
Ritonavir (Norvir)	600 mg twice daily	100-mg capsules	Gastrointestinal disturbances, perioral paresthesias
Nonnucleoside analogs			
Nevirapine (Viramune)	200 mg twice daily	200-mg capsules	Rash, diarrhea, drug fever
Delavirdine (U-90)	400 mg three times daily	Investigational	Rash, elevated liver enzymes

5. Because of problems related to drug failure over time, viral resistance, and drug toxicity, the initial use of combination drug regimens in HIV therapy is now recommended. AZT monotherapy is no longer the standard for initial therapy.
6. Triple therapy with two nucleosides plus a protease inhibitor appears to be the most potent antiretroviral regimen available.
7. Zidovudine/lamivudine may be better tolerated and appears to have comparable antiretroviral potency to other reverse transcriptase inhibitor combinations; however, there is some concern that initial lamivudine therapy, with resulting resistance mutations of reverse transcriptase, may impair later response to didanosine or zalcitabine, should they be required.
8. Although data support combination therapy, didanosine monotherapy is also a reasonable option, particularly for patients who cannot tolerate or who refuse combination therapy. This approach may allow adding zidovudine at a later time or switching to zidovudine/zalcitabine or zidovudine/lamivudine.
9. Stavudine/lamivudine is well tolerated, particularly for patients with limited bone marrow reserve who are poor candidates for zidovudine-containing regimens.
10. A protease inhibitor is often included in the initial regimen, particularly for patients at higher risk for progression.
 - a. A protease inhibitor could be added for symptomatic patients, patients with lower or rapidly falling CD4⁺ cell counts, and those with high plasma HIV RNA levels.
 - b. Saquinavir (600 mg tid) is well tolerated but has limited bioavailability and thus less potency.
 - c. Ritonavir (600 mg bid) is comparable in potency to indinavir; it has more frequent adverse effects including gastrointestinal disturbance (20-25% of patients), hepatotoxicity, and headache.
 - d. Indinavir (800 mg tid) is very potent and well tolerated. Toxic effects include benign hyperbilirubinemia and a 3-4% rate of nephrolithiasis.

II. Monitoring HIV Disease Progression

- A. Quantitative measurement of HIV RNA (i.e., viral load) by branched DNA or polymerase chain reaction testing provides a method of monitoring HIV disease.
- B. Plasma HIV RNA measurements are important for predicting risk of clinical progression, and combination therapies that reduce plasma HIV RNA levels are associated with increased survival and decreased progression to AIDS.
- C. HIV RNA levels are more predictive of progression than CD4⁺ counts, particularly in asymptomatic patients with cell counts higher than 350 cells/ μ L).
- D. HIV RNA levels are useful in assessing response to therapy. The therapeutic goal is a greater than 1 log reduction or a titer of less than 5,000 copies of HIV RNA/mL at 3 to 4 weeks after initiation of antiretroviral therapy. A 1 log decrease equates to a 10 fold reduction in RNA levels.
 1. If a significant reduction is not achieved, either adding or switching drugs is recommended.

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2. In some patients, a 0.5 log decrease may be the best achievable result. A 0.5 log decrease equates to a 3 fold decline in RNA levels.

E. HIV RNA viral load can be measured by two techniques, bDNA and polymerase chain reaction. Measurement techniques should be consistent because there is some variation in values depending on which method is used. bDNA may become the predominant method in use.

III. Changing Antiretroviral Therapy

A. Reasons for Changing Therapy: There are 3 primary reasons for changing antiretroviral therapy:

1. **Treatment failure.** Treatment failure is indicated by increases in viral load, decreases in CD4⁺ cell count or percentage, or clinical progression.
 - a. **Plasma HIV RNA level** should be measured 3 to 4 weeks after initiating or changing therapy, and then periodically on the same schedule as CD4⁺ cell counts (eg, every 3 to 6 months).
 - (1) The reduction in HIV RNA titer indicative of antiretroviral activity is a 1.0 log₁₀ decrease from the pretreatment value (about a 3-fold decrease) or a reduction of HIV RNA of >5,000 copies/mL.
 - (2) The HIV RNA levels measured within about 1 month after immunizations or active intercurrent illnesses may show transient elevations of 1.0 log₁₀ or more (a 10 fold increase).
 - b. **CD4⁺ Cell Count:** A return of CD4⁺ cell counts to greater than 20% below the baseline value on two consecutive visits at least 4 weeks apart is evidence of loss of drug effect.
 - c. **The occurrence of HIV-associated clinical complications** is considered evidence of treatment failure.
2. **Toxicity or intolerance.** All antiretroviral treatments are associated with dose-limiting toxic effects that occur more frequently with advanced disease.
3. **Current use of a suboptimal treatment regimen.** Zidovudine monotherapy is a suboptimal regimen and treatment should be reevaluated in any patient who is receiving it.

B. Changing Antiretroviral Therapy -- What to Change to

1. **If a Patient is Currently on Zidovudine Monotherapy:** Lamivudine (3TC) or didanosine (ddI) should be added to zidovudine; or the patient should be switched to didanosine monotherapy.
2. **In Patients with Advanced Disease and in those with Extensive Zidovudine Experience,** adding lamivudine to zidovudine or switching to another type of nucleoside analogue combination with a protease inhibitor may be beneficial.
3. In patients who have received a combination of 2 nucleoside analogues, such as zidovudine/didanosine, zidovudine/zalcitabine, or zidovudine/lamivudine, a change to combination therapy with at least 2 new drugs, such as 1 or 2 nucleoside analogues and a protease inhibitor is appropriate.
4. For patients for whom initial regimens included a protease inhibitor,

subsequent regimens should include at least 2 new drugs.

Options for Changing Therapy Due to Treatment Failure or Intolerance

Initial Regimen	Subsequent Regimen Options
Treatment Failure	
Zidovudine ⁺	Zidovudine/didanosine ± protease inhibitor Zidovudine/lamivudine (3TC) ± protease inhibitor Didanosine ± protease inhibitor Didanosine/stavudine ± protease inhibitor
Didanosine	Zidovudine/lamivudine (3TC) ± protease inhibitor Zidovudine/didanosine/protease inhibitor Stavudine/protease inhibitor
Zidovudine/didanosine	Zidovudine/lamivudine (3TC) ± protease inhibitor Stavudine/protease inhibitor
Zidovudine/zalcitabine	Zidovudine/lamivudine (3TC) ± protease inhibitor Stavudine/protease inhibitor Didanosine/protease inhibitor
Zidovudine/lamivudine (3TC)	Didanosine/protease inhibitor Stavudine/protease inhibitor Didanosine/stavudine Lamivudine (3TC)/stavudine
Drug Intolerance⁺⁺	
Zidovudine ⁺	Didanosine/stavudine Lamivudine (3TC)/stavudine
Didanosine	Zidovudine/lamivudine (3TC) Lamivudine (3TC)/stavudine Stavudine/protease inhibitor
Zidovudine/lamivudine (3TC)	Didanosine/protease inhibitor Stavudine/protease inhibitor Didanosine/stavudine

⁺Considered a suboptimal regimen; all patients on zidovudine monotherapy should be reevaluated.

⁺⁺A protease inhibitor (indinavir) could be added to the nucleoside analogue

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regimens listed.

IV. Special Considerations

A. Primary Infection

1. Primary HIV infection consists of the 4- to 7-week period of rapid viral replication immediately following exposure. Roughly 30-60% of individuals with primary infection develop an acute syndrome characterized by fever, malaise, lymphadenopathy, pharyngitis, headache, myalgia, and sometimes rash. Following primary infection, seroconversion usually occurs within 30 to 50 days.
2. A combination of at least 2 nucleoside analogues is recommended (eg, zidovudine plus either didanosine or lamivudine). A protease inhibitor is usually added. Treatment with 2 or 3 drugs is continued for at least 6 months and should probably be continued longer. After 6 months, consideration may be given to reducing the number of drugs to one or two.

B. Postexposure Prophylaxis

1. Risk of HIV transmission through occupational exposure is approximately 0.3% from a percutaneous injury from a needle or other device. The risk is significantly higher in deep, large volume, high titer exposures.
2. **Wound Decontamination:** The injury should be immediately washed and scrubbed with soap and water.
3. **Source Patient Testing:** The HIV status of the source patient is determined with the consent of the patient, or from the patient's stored blood if the patient refuses. (State laws may vary.)
4. **Recommendations for Post-exposure Prophylaxis:** Zidovudine 200 mg PO tid, plus lamivudine (3TC) 150 mg PO bid. Indinavir, 800 mg PO tid, is added if the source patient is AZT/3TC experienced.
5. Treatment is begun as soon as possible after exposure, and four weeks of therapy is recommended.
6. **Monitoring of Post-Exposure Prophylaxis:**
 - a. Monitor symptoms and exam, CBC and chemistry panel every 2 weeks while on treatment. Fatigue, nausea and headache are common. Hematologic toxicities are common and usually reversible, and they do not require discontinuation of therapy.
 - b. Follow-up serologies are checked at baseline, 6 weeks, 3 months, 6 months, and 12 months.

V. Primary Prevention of HIV Infection: Trials with subunit or recombinant vaccines are underway in uninfected recipients. It is likely to be several years until an effective HIV-1 vaccine is available for general use.

VI. Biological Basis of HIV Therapy

- A. The HIV virus is a retrovirus. The RNA genome of the virus uses the reverse transcriptase enzyme to make a DNA copy of the genome, which is then integrated into the host DNA.
- B. HIV related proteins require trimming by HIV protease before the virion is infectious.
- C. **Viral Natural History**
 1. HIV quickly infects a large number of T-lymphocytes bearing the CD4 surface antigen (CD4+ cells or helper cells).

2. HIV replicates extremely rapidly, but is slowed somewhat by the host immune response, and the viral titer stabilizes about six months after infection.
3. A high titer is associated with more rapid disease progression.
4. Continuous high-level viral replication occurs throughout the course of the disease. Half of the virus population in plasma is turned over within hours, which translates to billions of virions produced and destroyed daily. This extremely rapid replication rate gives the HIV virus the capacity to mutate to resistant forms and to spread in body.
5. Virus replication is almost matched by continuous generation of CD4 cells, but eventually HIV replication exceeds the rate of CD4 cell generation, and the CD4 cells become depleted.
6. The rate of virus replication stabilizes after primary infection at a particular level or "set point" in each individual. This level appears to be between 100 and 1,000,000 HIV RNA copies/mL of plasma, and this level remains relatively stable in asymptomatic patients over months and possibly years.

D. Disease Natural History

1. Following primary infection, seroconversion usually occurs within 30 to 50 days.
2. Two to four weeks after the primary infection, an acute syndrome develops in roughly 30% to 60% of individuals, characterized by fever, malaise, lymphadenopathy, pharyngitis, headache, myalgia, and sometimes rash. The acute clinical syndrome resolves in 2 weeks. This is followed by an asymptomatic period from infection to clinical symptoms that may last 11 years. However, 15% of patients progress to AIDS within 18 months of infection, and 5-10% may not progress to AIDS even after 10-15 years.

VII. Nucleoside Reverse Transcriptase Inhibitors

A. Zidovudine (ZDV, AZT, Retrovir)

1. Zidovudine is a nucleoside analog that is converted to the active triphosphate by cellular enzymes. Incorporation of zidovudine triphosphate into an elongating nucleic acid by reverse transcriptase is the primary mechanisms of action.
2. Zidovudine delays clinical disease progression in all disease stages below a CD4 cell count of 500/ μ L.
3. Beginning zidovudine before the onset of AIDS delays the progression of disease, as manifest by delayed onset of opportunistic infections, neurologic disease and neoplasms.
4. Subjective toxicities are common, including headache, nausea, lethargy, and malaise. Objective toxicities include anemia, neutropenia and, rarely, elevation of liver function tests. Myopathy is seen with prolonged treatment and at higher doses.
5. The dose of AZT is 200 mg tid. A combination tablet with 300 mg of AZT and 150 mg of lamivudine (3TC) makes twice a day combination therapy with these two drugs convenient.
6. Anemia and leukopenia due to zidovudine is common with prolonged administration. The use of growth factors such as recombinant erythropoietin, granulocyte-macrophage or granulocyte-colony stimulating factors may reduce zidovudine-induced bone marrow suppression.

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7. Treatment with zidovudine is discontinued if the hemoglobin drops to <8 g/dL or granulocyte counts <0.50 thousand/ μ L.
8. **Zidovudine Resistance**
 - a. Zidovudine resistance results from an accumulation of specific amino acid substitutions in the viral reverse transcriptase.
 - b. By 12 months on therapy, 89% of persons with late stage HIV-infection have zidovudine resistant isolates, compared with 31% with less advanced infection.

B. Lamivudine (3TC, Epivir)

1. Lamivudine is also a nucleoside analog. 3TC monotherapy induces rapid resistance secondary to mutations at reverse transcriptase. However, this same mutation appears to reduce AZT-resistance and restores AZT sensitivity if already established. Thus, combination therapy with AZT plus 3TC has shown substantial and prolonged benefit with no added toxicity. Prolonged HIV RNA suppression occurs at about 1 log compared to baseline.
2. 3TC is generally well-tolerated, although peripheral neuropathy and GI upset can occur. Adding 3TC to AZT does not add to substantially to the toxicity of AZT.
3. Standard dose is 150 mg BID. A combination tablet with 300 mg of AZT and 150 mg of 3TC makes twice a day combination therapy with these two drugs convenient.

C. Stavudine (d4T, Zerit)

1. Stavudine is a nucleoside analog that requires intracellular activation to a triphosphate for activity.
2. It is well-tolerated and is effective after prior AZT treatment.
3. Stavudine has little subjective toxicity (very well tolerated) and laboratory toxicities are uncommon.
4. Peripheral neuropathy is the most common objective toxicity but probably less than ddI or ddC. Pancreatitis does not occur.
5. Resistance development appears rare.
6. Standard dose 40 mg BID.

D. Didanosine (dideoxyinosine, ddI, Videx)

1. Didanosine is a nucleoside analog that is converted to the active, intracellular triphosphate.
2. Didanosine is effective after prior use of AZT. Didanosine is useful in advanced HIV-infection in individuals who are intolerant to, or who have failed zidovudine treatment.

3. Adverse Effects

- a. **Peripheral neuropathy** is a major dose limiting toxicity, and is characterized by symmetric distal numbness, tingling or pain.
 - b. **Pancreatitis**, ranging from mild abdominal pain and amylase elevations to fatal disease, occurs in 10% of individuals. Serum amylase and possibly lipase should be routinely monitored.
 - c. **Hyperuricemia** has been noted.
 - d. **Headache, diarrhea and GI intolerance** are commonly observed.
 - e. **Didanosine does not cause hematologic toxicities**, making it useful in patients with zidovudine-induced anemia.
4. **Dosage** for patients weighing 60 kg or more is 200 mg (given as two 100-mg tablets) bid or 250 mg of powder bid. For patients weighing less, the usual dosage is 125 mg (given as a 100-mg

tablet plus a 25-mg tablet) bid or 167 mg of powder bid; reduce dosage in renal failure. The powder, which contains antacid, is more palatable if taken with ice-cold water.

5. Oral bioavailability may be variable and the buffered tablets may interfere with absorption of other drugs dependent on gastric acidity (e.g., dapsone and ketoconazole).
6. **Resistance to Didanosine:** HIV-1 isolates with decreased susceptibility to didanosine have been documented following prolonged therapy, although the degree of resistance may be less than that seen with zidovudine.

E. Zalcitabine (dideoxycytidine, ddC, Hivid)

1. Zalcitabine is a nucleoside analog that requires intracellular activation to an active triphosphate for activity.
2. Zalcitabine has a clinical benefit equal to didanosine in patients who have failed zidovudine.
3. Zalcitabine is used infrequently because stomatitis (oral ulcers) and rash occur commonly during early therapy (2-6 weeks); these problems often can be treated symptomatically and subside despite continued treatment. Severe, painful peripheral neuropathy occurs in 7-15%. Pancreatitis has also been noted rarely.
4. Standard dose 0.75 mg TID
5. Zalcitabine-specific RT mutations have been reported. Some isolates resistant to didanosine have also been cross resistant to zalcitabine.

VIII. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)

- A. These compounds (e.g., nevirapine, delavirdine) bind directly to the reverse transcriptase enzyme complex and act to inhibit polymerization.
- B. Resistant viral mutants appear rapidly (within days to weeks) limiting their utility as monotherapy.

C. Nevirapine (Viramune)

1. The most common toxicities are rashes.
2. Rapid appearance of high level resistance is associated with drug failure.

D. Delavirdine (U-90)

1. Standard dose is not yet defined.
2. The most common toxicity is rash.
3. Resistance develops rapidly.

IX. Protease Inhibitors

- A. A viral encoded protease processes large viral polyproteins to yield functional structural proteins and enzymes essential for HIV replication. Protease inhibitors interfere with protease processing.

B. Saquinavir (SQV, Invirase)

1. Saquinavir is highly active against HIV, including zidovudine-resistant strains, and is synergistic when used concurrently with zidovudine, didanosine or zalcitabine.
2. Resistance develops, however, when the drug is used alone; strains that have become resistant to saquinavir are generally susceptible to indinavir and ritonavir.
3. The bioavailability of saquinavir is poor, which limits its effectiveness and may promote emergence of resistance.

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4. In patients with extensive previous zidovudine treatment, saquinavir plus both zidovudine and zalcitabine was more effective than saquinavir plus zidovudine or zidovudine plus zalcitabine.
5. Saquinavir is well tolerated; however, diarrhea, nausea and abdominal pain can occur.
6. Rifampin and rifabutin may lower saquinavir concentrations to ineffective levels. Saquinavir may interfere with metabolism of various other drugs, including terfenadine (Seldane) and astemizole (Hismanal), which in high concentrations can cause fatal cardiac arrhythmias.
7. Dosage is three, 200-mg capsules taken three times daily (1,800 mg/d) within two hours of a meal.

C. Ritonavir (Norvir)

1. A potent inhibitor of HIV, ritonavir is well absorbed and produces high concentrations in serum and lymph nodes. Saquinavir- and zidovudine-resistant HIV isolates are generally susceptible to ritonavir. When used in combination therapy, resistance to ritonavir develops slowly; strains resistant to ritonavir are cross-resistant to indinavir and saquinavir.
2. Adverse effects due to ritonavir are common and include nausea, vomiting, diarrhea, asthenia, circumoral and peripheral paresthesias, altered taste, and elevated triglycerides, cholesterol and hepatic transaminases.
3. Concurrent use of rifampin, rifabutin, dexamethasone or an anticonvulsant lowers serum concentrations of ritonavir. Ritonavir significantly affects the metabolism of many other drugs.
4. The dosage is 600 mg twice a day. Ritonavir should be taken with food. A liquid formulation has an unpleasant taste and is best taken with chocolate milk or a liquid nutritional supplement.

D. Indinavir (Crixivan)

1. Indinavir is also a potent protease inhibitor with good oral bioavailability. Resistance develops slowly; resistant strains are cross-resistant to ritonavir and saquinavir.
2. Serum HIV levels became undetectable after 24 weeks of treatment in 91% of patients treated with indinavir plus zidovudine plus lamivudine (3TC). Indinavir plus zidovudine and didanosine lowered HIV levels below the detectable range in 60%.
3. Indinavir is generally well tolerated. A mild elevation of indirect bilirubin occurs in about 10% of patients and usually resolves without intervention. Kidney stones develop in 3-4%, but in most cases the drug can be continued or restarted.
4. The dosage is 800 mg (two 400 mg tabs) tid. Patients should drink at least 48 ounces of water daily, and the drug should be taken with water, one hour before or two hours after a meal. Indinavir interacts with many other drugs, but fewer than ritonavir.
5. Indinavir lowers gastric pH and may interfere with absorption of didanosine; if used concurrently, the two drugs should be taken at least one hour apart.

References: See page 108.

Pulmonary Disease in the HIV-Infected Patient

I. Pathophysiology

- A. Pulmonary disease in HIV infection includes both infectious and noninfectious disorders. Factors that influence the frequency, morbidity and severity of pulmonary disease include the degree of immunosuppression as reflected by the CD4 lymphocyte count, environmental exposures, and use of chemoprophylaxis.
- B. Noninfectious pulmonary disorders associated with HIV infection include Kaposi's sarcoma, nonspecific interstitial pneumonitis, lymphoid interstitial pneumonia, and lymphoma.
- C. Pulmonary syndromes that occur in immunocompetent hosts may also occur in the setting of HIV infection. These include congestive heart failure, pulmonary emboli, and drug induced lung diseases.
- D. **Upper respiratory tract infections** are common in AIDS patients, especially sinusitis, which may present with headache, chronic cough, or fever of unknown origin (FUO). Symptoms of sinus congestion or drainage are often present.

II. Differential Diagnosis of Pulmonary Disease in HIV-Infected Patients

A. HIV-Associated Pulmonary Infections

Common	Less Common	Infrequent
Pneumocystis carinii Mycobacterium tuberculosis Pyogenic bacterial pneumonia	Cryptococcus neoformans Coccidioides immitis Histoplasma capsulatum Cytomegalovirus Nocardia	Aspergillus Legionella Mycobacterium kansasii Mycobacterium avium complex Toxoplasma gondii Cryptosporidium Strongyloides stercoralis Rhodococcus equi Moraxella catarrhalis Group D streptococcus

- B. Pneumocystis carinii pneumonia continues to be the most common HIV-associated pulmonary infection, even in the face of effective prophylaxis.
- C. PCP tends to have a subacute onset with gradually increasing shortness of breath, often over a period of weeks. The patient may complain of being unable to perform usual activities, such as carrying groceries up a flight of stairs.
- D. Bacterial pneumonias typically cause fever, purulent sputum, pleuritic chest pain, a lobar infiltrate on chest X-ray, and abundant organisms and neutrophils on Gram's stain.
- E. Mycobacterium tuberculosis and bacterial pneumonias also occur with increased frequency.
- F. Invasive fungal infections, CMV, and Nocardia, though less common, still warrant consideration. Aspergillus, atypical mycobacterium, and Legionella are infrequent pathogens.
- G. Susceptibility to HIV-associated pulmonary infections increases as the patient's CD4 count declines.
 1. Pneumocystis pneumonia occurs almost exclusively in patients with CD4 counts below 200.

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2. Other opportunistic pulmonary infections occur in advanced infection with CD4 counts below 50.
3. Exceptions to this general principle include Kaposi's sarcoma, mycobacterium tuberculosis, and nonspecific interstitial pneumonitis, all of which can occur in patients with normal or near normal CD4 counts.

III. Differential Diagnosis of Radiographic Patterns

- A. **Pneumocystis carinii pneumonia** is commonly associated with diffuse interstitial infiltrates, although a normal chest x-ray is found in 10% of cases. In patients who have been receiving aerosolized pentamidine prophylaxis, the chest x-ray may reveal upper lobe cavitory lesions or a pneumothorax. A pneumothorax in an HIV-infected patient is presumed to be *Pneumocystis pneumonia* until proven otherwise.
- B. **Bacterial pneumonias** are commonly associated with consolidation on chest x-ray.
- C. **Mycobacterium tuberculosis** typically presents as upper lobe cavitory in patients with early HIV disease, or it presents as miliary diseases or consolidation pneumonia in patients with advanced disease. Up to 25% of HIV patients with TB do not have any abnormality on chest x-ray other than subtle hilar adenopathy.
- D. **Kaposi's sarcoma** of the lung often appears as dense bilateral lower lobe infiltrates, often in association with pleural effusions. CT scan of the chest will often detect Kaposi's sarcoma at an earlier stage than chest x-ray.
- E. While the radiographic patterns may be helpful in narrowing the differential diagnosis, they are rarely diagnostic. HIV-related pulmonary infections can present with almost any radiographic appearance, including normal lung fields.

IV. Approach to Respiratory Disease in HIV-infected Patients with Advanced Disease (CD4 <200)

- A. Patients with respiratory symptoms and/or infiltrates on chest x-ray should receive sputum induction and empiric therapy for PCP.
- B. Sputum analysis should include a gram smear, routine culture, *Pneumocystis carinii* stain, and an acid-fast bacilli smear and culture. Using hypertonic saline to induce sputum increases diagnostic yield for *Pneumocystis*. The sensitivity for diagnosing *Pneumocystis* can exceed 90%.
- C. If sputum is diagnostic for PCP, specific therapy for PCP is continued.
- D. If sputum is nondiagnostic, bronchoscopy and bronchoalveolar lavage, and possibly transbronchial biopsy, are indicated.
- E. **Diffusing Capacity for Carbon Monoxide (DL_{CO})**: This test may be useful for patients with a clinical suspicion for PCP who have a normal or atypical chest x-ray.
- F. **High Resolution CT Scan**: Absence of typical changes (i.e. ground glass opacities) on this test may be useful to exclude PCP, but the test may be falsely positive.

V. *Pneumocystis Carinii* Pneumonia

- A. *Pneumocystis carinii* pneumonia (PCP) remains the most common serious opportunistic, even if PCP prophylaxis is used.
- B. The presentation can vary widely, from indolent disease, with symptoms developing slowly over days to weeks, to fulminant pneumonia evolving to severe respiratory compromise over just a few days.
- C. The risk for PCP begins at a CD4 count of about 200 cells/ μ L. PCP is more insidious than bacterial pneumonias. Patients with PCP complain of fever, night sweats, and dyspnea on exertion, progressing to dyspnea at rest. Spasms of nonproductive coughing are highly characteristic of PCP and are provoked by maximal inspiration.
- D. The chest x-ray typically reveals a diffuse, interstitial infiltrate, although some patients present with a normal film.
- E. To establish the diagnosis of *P. carinii* pneumonia, the organism must be visualized by induced sputum stain. For the patient who is still suspected of having *P. carinii* pneumonia whose induced sputum is negative, bronchoscopy with bronchoalveolar lavage is likely to yield the diagnosis.
- F. The choice of treatment depends on disease severity. A room air PO_2 of 70 mm Hg or an arterial/alveolar gradient of 35 mm Hg separates patients into favorable and unfavorable prognostic groups.
- G. **For patients presenting with a good level of oxygenation**, oral outpatient therapy can be instituted. Trimethoprim/sulfamethoxazole (Bactrim, Septra) is first-line therapy; 15-20 mg/kg/d of the trimethoprim component divided tid for 21 days. For patients who are sulfa-intolerant, other choices include dapsone, or aerosolized pentamidine. The addition of oral prednisone may improve the patient's tolerance for TMP/SMX. See "*Pneumocystis carinii* Pneumonia," page 97.
- H. **For patients presenting with significant hypoxemia**, parenteral therapy is initiated. Intravenous trimethoprim/sulfamethoxazole is first-line therapy, although pentamidine is equivalent. Adjunctive corticosteroids are given at the time of presentation. Antimicrobial and steroid therapy is continued for 14 to 21 days.
- I. If PCP is suspected but atypical bacterial pathogens are still a possibility, a macrolide may be added to TMP/SMX.

VI. Bacterial Pneumonias

- A. Bacterial pneumonias occur with increasing frequency in HIV-positive patients in late-stage disease who have CD4 counts below 200 cells/ μ L. However, they can occur earlier in some patients.
- B. Fever and productive cough are the principal symptoms, along with variable degrees of chest pain and dyspnea.
- C. The chest radiograph typically shows a focal infiltrate. The major exception is *H. influenzae* pneumonia, which may present as a diffuse infiltrate, similar to *P. carinii* pneumonia.
- D. In a patient with a focal infiltrate, the major organisms to cover empirically include *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *Staphylococcus* species, and perhaps *Legionella pneumophila*, *Klebsiella pneumoniae* and *Chlamydia pneumoniae*.
- E. Initial empiric therapy for pneumonia consists of a second- or third-generation cephalosporin such as ceftazidime, cefuroxime or ceftriaxone. Ampicillin may be used in low risk patients. If *L. pneumophila* or *C. pneumoniae* infection is suspected, a macrolide

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antibiotic such as erythromycin, clarithromycin or azithromycin is added.

- F. Treatment should be continued for 7-10 days, except in cases of *H. influenzae* pneumonia, which may require several weeks of parenteral therapy.

VII. **Mycobacterium Tuberculosis**

- A. Reactivation and acquisition of tuberculosis constitute another opportunistic infection. The reactivation rate for TB is 8-10% yearly.
- B. Reactivation disease takes on a more classical picture in patients with higher functioning immune systems (CD4 about 350 cells/ μ L). In patients with greater immunological impairment, classical cavitation may be absent. Infiltrates can be located in any area of the lung, accompanied by mediastinal and hilar adenopathy. Upper lobe cavitory disease is unusual, while diffuse interstitial and reticulonodular patterns are more common.
- C. Risk factors for TB include previous TB in close contacts, a prior positive tuberculin skin test result that was not treated, and previous residence in a jail or a hospital.
- D. Focal findings of a pneumonic process, such as rales or egophony may be present. Diagnosis of TB requires sputum smear and culture for acid-fast bacilli.
- E. All HIV-infected patients who present with a cough should be given approved masks to wear as soon as they check into a clinic or emergency department.
- F. Multi-drug regimens, with assured compliance, should be instituted when tuberculosis is suspected and diagnosed.

VIII. **Other Causes of Respiratory Disease**

- A. **Toxoplasma gondii** and **Cryptococcus neoformans** are less common infectious agents causing pneumonia.
- B. **Noninfectious complications** that may present as pneumonia include Kaposi's sarcoma, congestive heart failure secondary to HIV-related cardiomyopathy, and diffuse interstitial pneumonitis.

References: See page 108.

Oral Complications of HIV Infection

I. Oral Fungal Lesions

A. Candidiasis

1. The prevalence of oral candidiasis in HIV infection is high, with up to 15% of all HIV-infected patients being affected.
2. Oral candidiasis occurs more frequently as the CD4 count falls below 400 cells/ μ L.
3. *Candida albicans* is frequently part of the normal oral flora and is the most frequent cause of oral candidal infections.

4. Manifestations of Oral Candidiasis

- a. **Pseudomembranous candidiasis**, also called thrush, is characterized by the presence of white or creamy plaques on the oral mucosa; plaques can be removed, often revealing a bleeding surface.
 - b. **Erythematous candidiasis** appears as a flat red lesion that may be found on the hard or soft palate, dorsal surface of the tongue, or on other mucosal locations. When candidiasis affects the dorsal surface of the tongue, patchy depapillated areas appear.
 - c. **Angular cheilitis** may appear as cracking, fissuring, ulceration or erythema at the corner of the mouth.
5. Microscopic examination of a potassium hydroxide preparation will show hyphae and blastospores. Culture of the organism is not necessary.

6. Treatment of Oral Candidiasis

- a. Fluconazole (Diflucan), two 100 mg tablets are taken the first day, then once daily for 7-14 days. Fluconazole resistant candidiasis may occur.
- b. Ketoconazole (Nizoral), one or two 200 mg tablets are taken once daily with food. Ketoconazole may not be adequately absorbed in individuals with reduced gastric acidity, and it may cause liver toxicity.
- c. Oral topical medications include the use of topical troches or pastilles which are dissolved slowly in the mouth over 20-30 minute period.
 - (1) Clotrimazole (Mycelex) 10 mg troche, dissolved slowly in the mouth five times a day.
 - (2) Nystatin vaginal tablets 100,000 u, one tab dissolved 3 times a day; oral pastilles 200,000 units, one or two tablets dissolved in the mouth five times a day. Suspensions are not effective.
- d. Topical clotrimazole or ketoconazole creams or gels are useful for angular cheilitis.
- e. **Treatment Failure** is managed by increasing the dosage, changing to topical medications, or use of drug combinations.
- f. **Suppressive therapy** for oral candidiasis with fluconazole is not recommended because of the emergence of resistance to fluconazole.

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II. Virus Associated Oral Lesions

A. Oral Warts

1. Human papillomaviruses causes oral papillomas and focal epithelial hyperplasia.
2. Warts have a raised cauliflower-like appearance or are well-circumscribed with a flat surface.
3. Oral warts can be quite troublesome, with multiple lesions occurring throughout the oral cavity. They frequently recur after removal by laser, cryosurgery or knife.

B. Herpes Simplex

1. Herpes simplex can frequently produce recurrent painful episodes of ulceration, intraorally and circumorally. Lesions most commonly occur on the vermilion border and occasionally on the adjoining facial skin.
2. Intraoral lesions may appear on the palate or gingival margin. The patient reports small vesicles that erupt to form ulcers.
3. Diagnosis can be made by immunofluorescence testing, or by cytological smears showing characteristic viral giant cells (Tzanck preparation).
4. Recurrent HSV vesicles and ulcers that usually heal within ten days, but resolution of the lesions may take longer in advanced AIDS.
5. Acyclovir (200 mg 5 times/day) is effective. Acyclovir-resistant herpes simplex is usually sensitive to foscarnet.

C. Hairy Leukoplakia

1. Oral hairy leukoplakia (HL) is a white lesion of the oral mucosa, which is found predominantly on the lateral margins of the tongue, and sometimes on the buccal or lip mucosa and floor of the mouth, palate and oropharynx. Lesions range in size from a few millimeters to involvement of the entire dorsal tongue surface.
2. HL produces a white thickening of the oral mucosa that does not rub off; vertical folds or corrugations and projections give a "hairy" appearance. HL may extend onto the ventral surface of the tongue where it may appear flat and onto the dorsal surface of the tongue where it appears "hairy".
3. Epstein Barr Virus is readily demonstrated in HL; the lesion is not premalignant.
4. **Treatment:** If the lesions become extensive, uncomfortable or unsightly, acyclovir capsules, 800 mg taken four times a day for two weeks will usually result in disappearance of the lesion; lower maintenance doses may be necessary to prevent recurrence.

III. Neoplastic Disease

A. Kaposi's Sarcoma

1. The oral lesions of KS usually occur on the palate and gingiva. Other oral mucosal locations, notably the tongue, are also affected.
2. Oral lesions are purple or dark red and may be flat or nodular. A few are covered with a thick layer of uninvolved mucosa and therefore do not show abnormal color. Biopsy may be necessary for diagnosis.
3. Oral KS is usually asymptomatic unless the nodular stage becomes ulcerated when bleeding and pain from secondary infection may develop.
4. The oral lesions of KS should be treated if they become unsightly or

symptomatic, or if they interfere with oral function. Effective therapy includes laser or surgical excision, intra-lesional vinblastine (0.2-0.4 mg/ml/cm²), or localized radiation therapy.

IV. Other Lesions

A. Oral aphthous ulcers are common in AIDS patients. The cause is unknown, but hormonal factors, food allergy, stress and viral factors have been implicated. Antiretrovirals, especially zalcitabine, may cause oral ulcers.

1. The ulcers usually appear as painful, well-circumscribed, mucosal ulcers with an erythematous margin. Ulcers may become large with irregular margins.
2. Ulcers are usually of acute onset and heal in ten days to two weeks. The ulcers may persist for a month or longer and outbreaks may occur frequently.
3. Diagnosis may be made from the clinical appearance; however, the differential diagnosis includes squamous cell carcinoma, lymphoma, trauma, vesiculoerosive disease, herpes and syphilis. Biopsy may be necessary to determine the cause.
4. Treatment with topical fluocinonide (Lidex) ointment 0.05%, mixed with equal parts Orabase, applied 6 times daily, will usually shorten the duration of the ulcers. Fluocinonide gel 0.05% may be applied 3 times a day.
5. Three to four daily applications of a topical solution, alternating between 250 mg of tetracycline and 1 mg of dexamethasone, each dissolved in 5 ml of water may also be effective.
6. Thalidomide 200-400 mg/day is very effective; side effects include skin rash, neuropathy, and teratogenic potential.

V. Periodontal Disease

- A.** HIV-infected individuals have a tendency to develop severe gingival inflammation and progressive periodontal disease.
- B.** The gingiva appear bright red and swollen with ulcers at the tips of the interdental papillae. Pain is often severe and halitosis is common. Rapid and progressive destruction of the periodontal tissues and bone, with loosening of and even exfoliation of teeth, may ensue.
- C.** Treatment of periodontal disease should be referred to a dentist and involves removal of necrotic tissue, irrigation, and antibiotic therapy with metronidazole, ampicillin/sulbactam (Augmentin) or clindamycin.

References: See page 108.

Cytopenia in HIV Disease

Infection with HIV results in multiple disturbances of immune regulation and hematopoietic defects. Cytopenias develop frequently in patients with HIV infection, and myelosuppression is a major dose-limiting toxicity of many of the therapeutic agents used in the treatment of HIV and its associated diseases.

I. Severe Anemia

- A. Severe anemia (hemoglobin <8 g/d) occurs in approximately 25% of patients with AIDS, either as a result of hematopoietic defects from HIV infection or as a result of zidovudine therapy. Severe anemia often requires reducing the dosage of zidovudine and other myelosuppressive therapies.
- B. The most common form of zidovudine-induced anemia is megaloblastic anemia. The less frequent form is more similar to red cell aplasia.
- C. Erythropoietin is currently recommended for patients who develop anemia as a result of ZDV therapy. EPO has also been used for patients with HIV induced-anemia or anemia due to other myelosuppressive medications in patients with HIV infection and endogenous EPO levels greater than 500 mU/ml. The use of iron is also recommended.
- D. Patients with marrow infiltrating opportunistic infections, e.g., mycobacterium avium complex, or malignancies such as non-Hodgkin's lymphoma, may not respond to exogenously administered EPO. Failure to respond to this treatment warrants bone marrow aspiration and biopsy to exclude these possibilities as well as other hematologic diseases.
- E. Erythropoietin may be combined with myeloid hematopoietic growth factors such as G-CSF in patients with both neutropenia and anemia.
- F. Recombinant granulocyte colony-stimulating factor (G-CSF) has been shown to correct neutropenia in patients with HIV infection. Increases in neutrophil counts occur at doses of G-CSF between 100-200 mcg/m² administered subcutaneously daily.
 - 1. Increases in neutrophil counts are seen as early as 24 hours after initial injection.
 - 2. No evidence of marrow exhaustion has been seen with prolonged administration of this drug.
- G. Recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) at doses of 0.5-8 mcg/kg/day induces prompt dose-related increases in leukocyte numbers.

II. Thrombocytopenia

- A. Thrombocytopenia is both an early and late manifestation of HIV infection and may be due to myelosuppression from medications, infections, tumors, or increased peripheral destruction of cells such as with DIC, thrombotic thrombocytopenic purpura, or immune mediated thrombocytopenia.
- B. Discontinuation of myelosuppressive medications and treatment of infections and tumors can help correct thrombocytopenia.
- C. Plasma exchange or plasma infusion has been effective in some patients with TTP.

Gastrointestinal Disorders in HIV-Infected Patients

I. Gastrointestinal Symptoms Occurring in AIDS Patients

- A. Weight loss is universal
- B. Diarrhea: Nearly 70% of patients will note significant diarrhea
- C. Dysphagia or odynophagia occurs in 20-25% of patients
- D. Abdominal pain occurs in 1-2%
- E. Gastrointestinal hemorrhage occurs in 1-2%
- F. Jaundice occurs in 1-2%

II. HIV-Related Esophageal Disease

- A. Symptoms of esophageal disease include dysphagia (difficulty swallowing), odynophagia (painful swallowing), and esophagospasm (non swallowing pain).
- B. Painful swallowing indicates esophageal disease that can be so disabling that it leads to severe weight loss and malnutrition, accelerating the wasting syndrome. Risk for esophageal candidiasis begins at CD4 counts below 200 cells/ μ L.
- C. The same organisms or processes that cause oral lesions in patients with HIV infection also cause esophageal disease. *Candida albicans* is the most common cause of esophagitis.
- D. Other less common causes of esophagitis include herpes simplex virus and cytomegalovirus.

E. Treatment of Esophagitis

- 1. An empiric 2-3 week course of systemic oral fluconazole (Diflucan) is typically curative, although there is a high relapse rate following completion of therapy. Lifelong therapy with fluconazole is often required to prevent recurrence.
- 2. If systemic antifungal therapy is ineffective, empiric treatment for herpes with acyclovir may be prescribed.
- 3. Endoscopy with biopsy is used for patients who do not respond to empiric therapy.

F. Major AIDS-Related Esophageal Diseases

- 1. **Candida** is the most common cause of esophagitis.
 - a. It usually is associated with oral thrush.
 - b. Dysphagia is much more prominent than odynophagia.
 - c. Large yellow plaques are easily observed on endoscopy; biopsy is specific for disease.
 - d. Fluconazole is the drug of choice because its absorption is not altered by gastric pH. *Candida* is usually responsive to ketoconazole and itraconazole (however malabsorption of these drugs may occur in hypoacidic patients).
- 2. **Herpes Simplex** esophageal disease is infrequently seen in AIDS.
 - a. Prominent symptoms are odynophagia and esophagospasm, and pain is well-localized.
 - b. Ulcers occur early, and deep penetrating lesions occur later in disease.
 - c. Biopsy and culture are specific.
 - d. Lesions may be due to either HSV I or II. A favorable response to acyclovir usually occurs.
- 3. **Cytomegalovirus** esophagitis is very common
 - a. Occasionally the patient has known CMV disease elsewhere in

the body, such as CMV retinitis. Concomitant Candida may occur.

- b. The most prominent complaint is odynophagia (painful swallowing), which is more frequent than dysphagia. Occasionally severe painful esophagospasm is reported.
 - c. Endoscopic findings include large superficial and/or multiple ulcerations (usually distal). Diagnosis requires the presence of CMV inclusions plus vasculitis on biopsy.
 - d. Ganciclovir and foscarnet are effective but continuous maintenance therapy is required to prevent recurrence.
4. **Idiopathic ulcerations** of the esophagus are very common
- a. Large ulcers of the esophagus are seen that look similar to CMV ulcerations.
 - b. CMV and other agents should be excluded by endoscopic biopsy.
 - c. Lesions may respond to oral and/or intralesional steroids.

III. HIV-Related Stomach Diseases

- A. **Symptoms** of stomach disease include nausea, vomiting (early postprandial), early satiety, late postprandial emesis, hematemesis, and epigastric pain.
- B. **Non-AIDS diseases** are frequently found, including acid peptic ulcer, pancreatitis, gastritis, cholangitis, variceal hemorrhage, Mallory-Weiss tears, and retroperitoneal adenopathy.
- C. **Kaposi's Sarcoma** is the most common AIDS condition found in the stomach.
 1. 40% of patients with cutaneous KS have visceral disease.
 2. Biopsy confirms the diagnosis.
 3. Rare complications in AIDS patients include obstruction, hemorrhage, and perforation.
- D. **B cell type Lymphoma**
 1. Gastric lymphoma remains usually limited to the stomach; however, there sometimes may be extensive disease throughout the abdomen.
 2. Occasionally there is obstruction or hemorrhage, and lesions may perforate with intensive chemotherapy.
 3. Diagnosis is by biopsy.
- E. **Other Conditions**
 1. Helicobacter pylori may be decreased in prevalence among AIDS patients. It causes gastritis, and usually responds to triple therapy with antibiotics.
 2. CMV may cause large gastric ulcerations that usually occur in the proximal stomach.

IV. HIV-Related Hepatobiliary Disease

- A. Symptoms include right upper quadrant abdominal pain, fullness, jaundice (rare), spiking fevers, and biliary colic.
- B. **Biliary Tract Disease**
 1. **Acalculous Cholecystitis** is most commonly caused by CMV and cryptosporidiosis. A cholecystectomy is indicated to exclude gallstone disease or obstructive duct disease.
 2. **AIDS Cholangiopathy**
 - a. This disorder is usually associated with right upper quadrant pain and fever; the patient is not icteric (mean bilirubin 1.3 mg/dL). The ultrasound and CT scan are usually abnormal, but 20% have

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normal studies.

- b. The alkaline phosphatase is markedly abnormal (788 IU/L). Diagnosis is by direct cholangiography.
- c. Idiopathic inflammation is the most common cause of cholangiopathy, followed by CMV and cryptosporidium. Other less common causes include *Mycobacterium avium* complex, Kaposi's Sarcoma, and lymphoma. Microsporidiosis has been detected in the biliary duct.
- d. Gallstones and strictures that may mimic cholangiopathy must be excluded.
- e. **Therapy:** Sphincterotomy often provides a favorable pain response for patients with papillary stenosis.

V. Pancreatitis

- A. Pancreatitis may be triggered by TMP/SMX, other sulfa drugs, IV pentamidine, or antiretroviral agents such as didanosine (ddI). Symptoms may resolve if medications are withdrawn.
- B. CMV and MAC have also been implicated in AIDS-related pancreatitis, but because the pancreas is rarely biopsied, the underlying cause often cannot be determined.

VI. HIV-Related Small Bowel Disease

- A. Probably 75 to 80% of patients have a specific pathogen; however, definitive diagnosis may require extensive invasive procedures.
- B. Symptoms include cramping, para-umbilical pain, weight-loss, steatorrhea, and large volume dehydrating diarrhea.

VII. HIV-Related Colorectal Disease

- A. Symptoms of colorectal disease include lower quadrant pain; particularly in the left lower quadrant. Small volume diarrhea is common, but rarely dehydrating. Incontinence, tenesmus (extreme urgency), proctalgia, dyschezia, and hematochezia may be noted.
- B. **Common Pathogens**
 - 1. Routine bacterial and parasitic enteric pathogens
 - 2. Parasites
 - 3. CMV - ischemic-like lesions on endoscopy
 - 4. Herpes - large extremely painful anal lesions
 - 5. Idiopathic perirectal ulcerations
 - 6. Other causes include anal cancer, condylomata, perirectal abscesses, hemorrhoids, fissure, underlying inflammatory bowel disease.

VIII. Gastrointestinal Diseases Due to Cytomegalovirus

- A. Cytomegalovirus (CMV) ulcerative disease most frequently occurs in the gastrointestinal tract, occurring anywhere from the esophagus to the sigmoid colon.
- B. Symptoms may include odynophagia with esophageal disease, epigastric pain with gastric disease, poorly localizing pain with small bowel disease, and pain and tenderness in the right and left lower quadrants with colonic disease.
- C. Definitive diagnosis is by endoscopy and biopsy. Treatment consists of ganciclovir or foscarnet.

IX. HIV Enteropathy

- A.** HIV enteropathy may manifest as poorly-localized, non-organ-specific GI symptoms, including anorexia, nausea, weight-loss, large volume diarrhea (>1-2 liters/day), and paraumbilical cramping pains.
- B.** These symptoms are probably related to generalized "mid-gut" GI tract disease (small bowel) from HIV infection of enterocytes.

References: See page 108.

Diarrhea in HIV-Infected Patients

The gastrointestinal tract is one of the major target organs of HIV-related disease, and diarrhea is reported in up to 60% of patients with AIDS. Most HIV-infected patients with diarrhea have some degree of malabsorption and many are also malnourished. Episodes may wax and wane over time, and in at least 30% of patients, an etiology cannot be determined. In such cases, the diarrhea is often attributed to HIV itself, and empiric therapy must suffice.

I. Clinical Evaluation of AIDS-Associated Diarrhea

- A. The history should include the duration of symptoms, frequency and characteristics of stools, and the CD4 count. Quantitate the amount and rate of weight loss. Determine residential exposures, occupational exposures, recent travel, pets, hobbies (i.e., fishing, hunting, cooking), and water supply.
- B. Recent antibiotic or antiretroviral use, previous opportunistic infections, and other illnesses or hospitalizations should be assessed.
- C. Presence of sexually transmitted diseases, intake of unpasteurized dairy products, raw or under-cooked meat or shellfish, or organic vitamin preparations should be sought.
- D. **Small-bowel diarrhea** is generally watery and occurs in large volume (up to 10,000 mL/day).
 - 1. Abdominal cramping, bloating, gas, and potentially profound weight loss may occur.
 - 2. Fever is absent and stool examinations for occult blood and fecal leukocytes are negative.
- E. **Large-bowel Disease** is characterized by frequent, regular, small-volume, often painful bowel movements. Fever and bloody or mucoid stools are common, and fecal leukocytes are positive.
- F. **Systemic Diseases**, such as disseminated *Mycobacterium avium* infection, may present with diarrhea prominent among other symptoms, including persistent fever, severe weight loss and symptomatic anemia.

CD4 Count as a Predictor of Pathogens Causing Diarrheal Disease

Pathogen	Absolute CD4 count	
	≥200	<100
Bacteria	Salmonella Shigella Campylobacter Yersinia Clostridium difficile Mycobacterium tuberculosis	Escherichia coli Mycobacterium avium
Viruses	Adenovirus Rotavirus Herpes simplex virus ? HIV	Cytomegalovirus
Protozoa	Giardia lamblia Entamoeba histolytica	Microsporidium Cryptosporidium Isospora Cyclospora
Fungi	Histoplasma	Cryptococcus

II. Physical Examination

- A. Height and weight, temperature, orthostatic blood pressure, and degree of wasting are documented.
- B. Skin and mucous membrane abnormalities may reflect underlying nutrient deficiencies. Dermatitis may suggest zinc deficiency and stomatitis may suggest vitamin B-12 deficiency.
- C. CMV retinitis raises the possibility that gastrointestinal disease may be due to CMV as well.
- D. Organomegaly detected on abdominal examination may be the first sign of disseminated mycobacterial infection, histoplasmosis or lymphoma.
- E. Neurologic examination should include an assessment of long tract function (vibration and position sense) which may uncover vitamin B-12 deficiency.

III. Laboratory Evaluation of Diarrhea

- A. Initial evaluation consists of stool cultures for enteric organisms, an assay for *C. difficile* toxin, a fecal leukocyte count, and examination for ova and parasites.
- B. **Blood cultures for bacteria** are appropriate in febrile patients, when the suspicion for bacterial enteritis (i.e., *Salmonella*) is high.
- C. **In febrile patients with a CD4 cell count <200, two sets of blood cultures** for mycobacteria or fungi should also be submitted.
- D. Modified acid-fast smear for cryptosporidia is appropriate in patients with very low CD4 cell counts and severe diarrhea.
- E. If the initial evaluation is negative, the studies should be repeated once or twice more in case a pathogen was missed. If these tests are negative and diarrhea persists, options include flexible sigmoidoscopy or colonoscopy and treating empirically with antidiarrheals. Biopsy may reveal evidence of CMV, MAC, or herpes simplex and may also be helpful in evaluating for microsporidia, cryptosporidia, and, rarely, *Giardia lamblia*.

IV. Symptomatic Treatment of Chronic Diarrhea

- A. Loperamide (Imodium) 4 mg po initially, then 2 mg q6h around the clock and prn (maximum 16 mg qd).
- B. Diphenoxylate-atropine (Lomotil) 2.5-5 mg po 3-6 times daily for 24-48 hr, then 2.5-5 mg tid and prn to control diarrhea (maximum 20 mg qd).
- C. Paregoric 0.4 mg morphine/mL, 5-10 mL qd-qid.
- D. Octreotide (Sandostatin) 100 mcg SQ tid, increase by 100-200 mcg q1-2 weeks until maximum of 500 mcg SQ tid or until 50% decrease of stool output.

V. Bacterial Small-bowel Pathogens

A. *Salmonella*

- 1. *Salmonella* can involve either the small or large bowel or both, but it often causes watery, non-bloody, non-mucoid diarrhea typical of small-bowel disease. Fever is often present.
- 2. Non-typhoidal *Salmonella* infection, with or without bacteremia, can develop before and after the diagnosis of AIDS.
- 3. Blood cultures should be submitted when this diagnosis is suspected.
- 4. Relapses are common without maintenance therapy. Antibiotics

active against *Salmonella* (i.e., trimethoprim-sulfamethoxazole, fluoroquinolone) prevent relapse.

B. Mycobacteria

1. *Mycobacterium avium* complex and *Mycobacterium tuberculosis* both cause systemic infections in AIDS, although *M. avium* is much more commonly associated with diarrheal disease. MAC is highly prevalent in AIDS, affecting as many as 25% of patients.
2. Disseminated *M. avium* infection generally occurs several months after the diagnosis of AIDS has been established. Mean CD4 counts are in the range of 60 cells/ μ L, and infection in those with counts >100 cells/ μ L is rare.
3. Malabsorptive diarrhea generally occurs in systemic illness, with persistent fever and weight loss associated with infiltration of the small bowel by MAC.
4. Focal lesions of the gastrointestinal tract often involve the duodenum, and organisms characteristically disseminate to bone-marrow, liver, spleen and lymph nodes.
5. Blood cultures will diagnose this disorder and they are 98% sensitive if two samples are submitted. Neither a positive stool culture for MAC nor the presence of acid-fast organisms on smear is diagnostic of bowel infection by the organism. However, the latter is strongly suggestive of intestinal infection.

VI. Protozoa Small Bowel Pathogens

A. Cryptosporidium enteritis most often occurs in patients with AIDS, and it is the most common cause of diarrhea in this group, accounting for up to 16% of cases.

1. Most patients present with typical small-bowel disease characterized by large-volume non-bloody diarrhea, nausea, vomiting, abdominal pain, and weight loss. Gastric outlet obstruction, colitis and toxic megacolon may occur.
2. Cryptosporidia is one of the more common causes of chronic, seemingly pathogen-negative diarrhea.
3. CD4 counts >180 cells/ μ L are associated with spontaneous resolution of diarrhea within 1-4 weeks. However, counts <180 cells/ μ L are associated with persistent disease.
4. Modified Ziehl-Neelsen or immunofluorescence staining of a stool sample generally reveals the pathogen.

B. Microsporidia

1. Patients generally experience chronic, intermittent, watery, non-bloody diarrhea and weight loss without fever or abdominal pain.
2. Patients with symptomatic microsporidiosis of the small bowel usually have CD4 values of <30 - 35 cells/ μ L. Therefore, the initial evaluation of diarrhea in HIV-infected patients with CD4 counts above 100 cells/ μ L need not include tests for Microsporidia.
3. Modified trichrome and chitin stains are effective in screening for intestinal microsporidial infection.

C. Isospora belli

1. *Isospora belli* causes a chronic diarrheal syndrome indistinguishable from that caused by Cryptosporidia.
2. Infection with this pathogen is rare in the United States, and those affected are primarily recent immigrants from Mexico, Latin and Central America.
3. Eosinophilia and an appropriate exposure history in an AIDS patient

with diarrhea should suggest the possibility of infection with *I. belli*.

VII. HIV Small Bowel Enteropathy

- A.** HIV itself may be responsible for "pathogen-free" chronic diarrhea in AIDS.
- B.** There appears to be a subset of HIV-infected patients with relatively intact immune systems who develop chronic diarrhea in the absence of identifiable pathogens.
- C.** An exhaustive search for a pathogen should be undertaken before attributing diarrheal disease to HIV enteropathy.

VIII. Bacteria Large-bowel Pathogens

A. Shigella

- 1. *Shigella* causes bacillary dysentery, and presents with the typical colitic syndrome of abdominal cramping, tenesmus and frequent small-volume bloody stools.
- 2. Fever is present in 50% of the patients. Bacteremia is relatively uncommon in immunocompetent adults, but more frequent in HIV-infected patients.
- 3. HIV-infected patients are not particularly predisposed to infection with *Shigella*, the incidence being no different than in the non-HIV-infected homosexual population.

B. Campylobacter

- 1. *Campylobacter* occasionally involves the small bowel, but usually causes proctocolitis, with cramping and bloody diarrhea. Fever is often absent. In HIV-infected patients, *Campylobacter* is distinctive in its ability to cause prolonged diarrhea.
- 2. *Campylobacter* enteritis may present with negative stool cultures in HIV-infected patients, and cultures of biopsy specimens may be necessary to make the diagnosis.

C. Clostridium difficile: This bacterium causes antibiotic-associated diarrhea and life-threatening pseudomembranous colitis.

D. Vibrio parahaemolyticus

- 1. This bacterium is an important cause of acute colitis related to the ingestion of inadequately cooked or raw seafood.
- 2. *V. parahaemolyticus* is identified more frequently in homosexual men with AIDS.

E. Enterohemorrhagic or Verocytotoxin-Producing E. coli

- 1. These agents are responsible for hemorrhagic colitis, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Outbreaks and sporadic cases have been reported.
- 2. This pathogen should be considered in AIDS patients with gastrointestinal symptoms, especially if renal failure or hematologic abnormalities are present.

IX. Viral Large Bowel Pathogens

A. Cytomegalovirus

- 1. CMV, a member of the herpesvirus group, is almost ubiquitous in patients with AIDS.
- 2. CMV infection most commonly manifests as retinitis. However, it can also cause encephalitis, pneumonia, hepatitis, adrenalitis and sinusitis, as well as gastrointestinal disease.
- 3. Risk for developing CMV disease increases when the CD4 count falls below 100 cells/ μ L.

4. CMV can occur anywhere from the mouth to the anus and can cause panenterocolitis in patients with AIDS. The colon is the most common site of gastrointestinal involvement.
5. Symptoms of CMV colitis include chronic diarrhea, crampy abdominal pain, weight loss, hematochezia and fever.
6. Only 30% of patients with CMV colitis have positive blood cultures at the time of diagnosis.
7. The diagnosis of CMV colitis is definitively made by biopsy of abnormal colonic mucosa with demonstration of the classic nuclear inclusions.

References: See page 108.

Neurologic Complications of HIV Infection

About 40 percent of patients with AIDS or symptomatic HIV infection develop a neurologic syndrome. Approximately half the neurologic manifestations are due to the effects of HIV on the nervous system and half are the result of opportunistic or secondary complications of immune deficiency.

I. Diagnostic Approach to Headache in the HIV-Infected Patient

A. When headache occurs in the HIV-infected patient, the state of cellular immunity should be determined.

1. Immunocompetent patients with a CD4 count >500, no prior opportunistic infections and no clinical signs of immunosuppression

a. These patients should be evaluated similarly to non-HIV infected patients.

b. **Migraine or sinusitis** should be considered.

c. **If headache, fever and meningismus are present:** CSF analysis should be completed (in the absence of focal neurologic signs or papilledema). In addition to the usual CSF tests, an India ink prep, cryptococcal antigen, and fungal culture should also be obtained.

(1) Abnormal CSF findings may be diagnostic for aseptic meningitis, cryptococcal meningitis, and other forms of meningitis.

(2) If the CSF is normal, a MRI or CT is completed.

2. Immunodeficient patients with headache and a CD4 count <500, previous opportunistic infections, oral thrush, or weight loss

a. These patients should be evaluated for opportunistic CNS infections and processes.

b. If focal signs are present in these patients, a MRI or CT should be completed. Focal lesions on MRI or CT, especially if enhancing, usually lead to empiric therapy for toxoplasmosis. Absence of focal lesions should lead to CSF analysis.

c. If focal signs are absent in these patients, CSF analysis should be performed.

(1) Abnormal CSF findings may be diagnostic for aseptic meningitis, cryptococcal meningitis, and other forms of meningitis.

(2) If the CSF is normal, MRI or CT is completed.

II. Diagnostic Approach to Altered Mental Status, Focal Signs or Seizures in the HIV-Infected Patient

A. In AIDS patients with CNS symptoms such as altered mental status, focal signs or seizures, a CNS brain abscess should be sought with an MRI or CT scan.

1. **Atrophy or diffuse white matter disease** indicates HIV dementia.

2. **Single or multiple focal lesions that contrast-enhance** should be considered to be toxoplasmosis or CNS lymphoma, and empiric toxoplasmosis therapy should be initiated.

a. If no improvement occurs after 10-14 days of toxoplasmosis therapy, a brain biopsy should be considered.

b. Improvement after 7 days of toxoplasmosis therapy usually confirms toxoplasmosis.

3. **Non-enhancing focal lesions with no mass effect, located in the cortical white matter**, indicate progressive multifocal encephalopathy.
4. **Non-enhancing cystic lesions in the basal ganglia are indicative of Cryptococcosis**, which can be confirmed by CSF analysis.
5. **Periventricular inflammation** on MRI, indicates CMV encephalitis.

III. HIV-Related Meningitis

- A. One or two percent of recently HIV-infected persons develop an acute aseptic meningitis, with headache, meningismus, cranial neuropathies, and occasionally transient encephalopathy.
- B. Thirty percent of HIV carriers have a more indolent variant of HIV-related meningitis with chronic headaches and pleocytosis of the CSF fluid.
- C. The acute symptoms of HIV-related meningitis usually require only symptomatic treatment with analgesics, and they resolve within a few weeks.

IV. AIDS Dementia Complex (ADC)

- A. Immune system compromise often is accompanied by cognitive and motor changes ranging from mild impairment to dementia approaching the severity of Alzheimer's disease. ADC develops gradually over weeks to months in the absence of fever.
- B. Early disease is characterized by difficulty concentrating or completing tasks that had been routine and by forgetfulness, feeling "spaced out," or having difficulty functioning efficiently at work.
- C. Full-fledged dementia generally is associated only with advanced AIDS. The prevalence of dementia in patients with frank AIDS is 5-15%.
- D. ADC is largely a diagnosis of exclusion. Other causes of neuropsychological disturbance such as CNS infection, lymphoma, or substance use or withdrawal must be excluded.
- E. Evaluation includes a history and a physical exam with a careful neurologic evaluation.
- F. A serum VDRL, cryptococcal antigen assay, lumbar puncture, and MRI of the brain should be completed.
- G. MR imaging shows cerebral atrophy and widened cortical sulci and enlarged ventricles. Basal ganglia are reduced in volume. MR demonstrates diffuse or multifocal increase in T2 weighted signal in the white matter; the frontal lobes are particularly involved.

H. Neuropsychological Testing

1. **The Mental Alternation Test** is a quick bedside test for dementia. The patient is asked to alternate between numbers and the alphabet in order: 1-A, 2-B, 3-C, etc. This test is more sensitive than the Mini-Mental State Exam in detecting dementia. Tests of psychomotor speed (Grooved Pegboard, Trailmaking Test) and memory are also sensitive for early HIV dementia.
2. The Mini Mental Status Examination is not sensitive for detection or monitoring of neurocognitive status.
3. The diagnosis of dementia requires that the patient exhibit difficulties with memory and one other area of mental functioning, such as aphasia, apraxia, or a decrease in the executive functions of judgment, synthesis and action.
4. The condition must have a significant impact on the patient's life,

usually involving the inability to work and care for oneself.

5. AIDS dementia is an AIDS-defining condition.

I. Management of AIDS Dementia Complex

1. Treatment of AIDS dementia consists of aggressive antiretroviral therapy aimed at reversing HIV-related immunosuppression. High dose zidovudine (Retrovir), 800 mg daily is the most commonly used drug.
 - a. Because dementia frequently develops in patients who have already used zidovudine for prolonged periods, an alternative agent is didanosine (Videx), given in doses of 150-300 mg twice daily.
 - b. Previously untreated patients with mild or moderate HIV-dementia often show improvement in memory and psychomotor speed within a few weeks. Unfortunately, the clinical benefits are usually limited to a few months and the disorder then progresses again.
2. Apathy may respond to methylphenidate (Ritalin), starting with 5 mg twice a day; there is a risk of seizures.
3. If marked depressive symptoms are present, tricyclic antidepressants can be tried in 25-50% of the usual dose. Selective serotonin reuptake inhibitors, such as fluoxetine (Prozac) 10-20 mg qAM, are useful because of their slight stimulant effects.
4. Psychoactive drugs, hypnotics and anxiolytics should be avoided or used only in reduced doses because patients with HIV dementia are extremely susceptible to the adverse effects of these agents.

V. HIV-Associated Myelopathies

- A. **A noninflammatory vacuolar myelopathy** may affect 20% of patients with AIDS, manifesting as progressive spastic paraparesis and sensory ataxia, often accompanied by progressive dementia.
- B. **HTLV-4**, a retrovirus, may infect patients with HIV infection causing a progressive myelopathy, and it can be excluded by serologic testing.
- C. **Structural or compressive lesions and correctable nutritional deficiencies** such as vitamin B12 deficiency should be excluded. A discrete sensory level and localized back pain or percussion tenderness are not consistent with myelopathy, and an MRI of the spine or myelography should be used to exclude an epidural abscess or tumor.
- D. Myelopathy is commonly associated with a mild elevation of CSF protein and pleocytosis (5 to 20 leukocytes). A more inflammatory CSF profile should prompt a search for a herpesvirus myelitis or neurosyphilis.
- E. Antiretroviral therapies have not been useful in reversing myelopathy, which usually progress inexorably. Antispasticity agents such as Lioresal (Baclofen) may be useful.

VI. Peripheral Nerve Disorders Associated with HIV Infection

A. Sensory Neuropathy

1. Thirty percent of patients with AIDS develop a neuropathy characterized by painful sensory symptoms in the feet. Most patients develop this neuropathy late in the course of HIV infection, usually in association with systemic opportunistic infections.

2. Complaints include dysesthesias and contact hypersensitivity in the feet, associated with reduced or absent ankle reflexes and elevated vibratory thresholds and hyperalgesia.
3. Electrophysiologic studies usually reveal a neuropathy of sensory and motor fibers. Nerve biopsy usually is not necessary in this clinical setting.
4. A sensory neuropathy due to alcohol, diabetes, pyridoxine excess, vitamin B12 deficiency, and neurotoxic antiretroviral agents (such as didanosine, dideoxycytidine, or lamivudine) should be excluded when patients develop painful sensory symptoms.

5. Treatment of Sensory Neuropathies

- a. Nonsteroidal anti-inflammatory drugs, acetaminophen in combination with oxycodone, hydrocodone or codeine, and stronger agents such as morphine sulfate are used.
- b. Tricyclic antidepressants such as amitriptyline (Elavil) or nortriptyline (Pamelor) may help relieve pain. Treatment begins with a small dose (e.g., nortriptyline, 10 mg twice a day) and is increased slowly. Carbamazepine and mexiletine have been used.
- c. Topical agents such as capsaicin (Zostrix-HP) are not useful. For constant burning dysesthesias, 30% lidocaine cream may provide transient relief.

B. Inflammatory Demyelinating Polyneuropathies

1. Inflammatory demyelinating polyneuropathies (IDPs) are immune mediated phenomena characterized by profound motor weakness, which sometimes develops acutely as Guillain-Barré syndrome.
2. In contrast to HIV-related sensory neuropathy, IDPs typically occur at a relatively early stage of HIV infection, before immunodeficiency develops.
3. The treatment of choice is plasmapheresis.

C. Cytomegalovirus Radiculopathy

1. CMV can cause a progressive radiculopathy involving lumbar and sacral roots.
2. This disorder is associated with advanced immunodeficiency with a CD4 count below 100 and CMV infection at other locations (retinitis). The radiculopathy slowly develops over 1-4 weeks and is associated with a polymorphonuclear pleocytosis; CMV can often be cultured from the CSF.
3. Ganciclovir (Cytovene) can reverse the radiculopathy if treatment is started before paralysis is complete. Ganciclovir is initially given at a dose of 10 mg/kg/day in two doses for 14 days, followed by daily IV infusion of 5 mg/kg as maintenance.

D. Herpes Zoster Radiculitis

1. Five to ten percent of patients with HIV infection develop radiculitis.
2. Dermatomal herpes zoster does not require specific treatment unless located in multiple cervical or lumbar dermatomes. In the cervical and lumbar dermatomes, the potential exists for severe myeloradiculitis with permanent motor deficits, and IV acyclovir (30 mg/kg/d) should be administered.
3. Post-herpetic neuralgia may require pain-modifying agents such as amitriptyline (Elavil) or carbamazepine. After the vesicles have completely healed, topical capsaicin (Zostrix) can reduce neuralgic pain.

E. Myopathies

1. **Polymyositis** is an uncommon muscular complication of HIV infection that is characterized by myalgias, weakness, greatly elevated serum creatine phosphokinase (CPK), and an abnormal muscle biopsy. The disorder sometimes responds to corticosteroids or IV immunoglobulin
2. **Zidovudine Myopathy** may occur after prolonged use for more than 6-12 months. The clinical features of toxic myopathy are indistinguishable from those of polymyositis. If a zidovudine drug holiday of 2 to 4 weeks is accompanied by clinical improvement in myalgias and a drop in CPK, a toxic myopathy is the likely diagnosis, and an alternative antiretroviral, such as didanosine, should be used.

VII. Opportunistic Neurologic Processes

- A. Opportunistic infections and neoplasms of the CNS are common in association with HIV.
- B. Opportunistic processes usually do not develop until the CD4 count is below 200 cells/ μ L.

C. Intracranial Focal Lesions

1. A variety of disorders can cause intracranial focal lesions, including toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy (PML), cryptococcosis, and other bacterial and fungal infections.
2. In AIDS patients with altered mental status, headache, focal signs, seizures or other signs of a CNS brain abscess, a presumptive diagnosis via brain imaging should be made.
3. MRI is more sensitive than CT at detecting the multiple and ring-enhancing lesions of toxoplasmosis encephalitis.

D. Cryptococcal Meningitis

1. *Cryptococcus neoformans*, a ubiquitous yeast, produces CNS infection in about 10% of patients with AIDS.
2. The risk for developing Cryptococcal *neoformans* meningitis begins at a CD4 count below 100 cells/ μ L.
3. The most common presentation consists of headache, meningismus, altered mentation, cranial neuropathies, fever, and vomiting developing over days. This disorder can mimic bacterial meningitis, toxoplasmosis, other opportunistic processes, and HIV dementia.
4. Meningismus is much less seen in cryptococcal meningitis than in bacterial meningitis. Severe cases are associated with altered mental status and papilledema.
5. Cryptococcomas can form mass lesions that are usually located in basal ganglia and are not enhancing.
6. India ink preps have a sensitivity of about 80% and can rapidly lead to the diagnosis of cryptococcal meningitis. However, in the face of a highly suspicious history and exam, a negative India ink prep should not dissuade one from the possibility of cryptococcal meningitis.
7. Patients with proven disease will almost always have positive serum and cerebrospinal fluid cryptococcal antigen titers and such patients will have positive fungal cultures.
8. The cerebrospinal fluid may often appear remarkably noninflammatory with a normal protein and WBC count, despite

the presence of overwhelming infection.

9. Treatment of Cryptococcal Meningitis

- a. Amphotericin B, 0.7 mg/kg per day for 7 to 14 days or until clinically stable (to a total dosage of 1 g), followed by fluconazole 400 mg qd to complete 10 weeks of therapy.
- b. During successful treatment, both serum and CSF cryptococcal antigen titers can be expected to fall by at least four dilutions and fungal cultures become negative.
- c. The CSF should be reexamined at the end of induction therapy or if there is recrudescence of symptoms. Persistently positive fungal cultures imply failure or relapse. The cryptococcal antigen titer can remain positive, and this does not imply treatment failure.
- d. Relief of highly elevated CSF, spinal tap, opening pressures by repeated spinal taps or by placement of a catheter into the spinal canal for monitoring and removal of fluid, may be needed.
- e. Suppressive treatment with fluconazole (Diflucan), 200 mg daily, is necessary for lifelong maintenance.

E. Cytomegalovirus Encephalitis and Retinitis

1. CMV retinitis causes vision loss in up to 20% of patients with AIDS if left untreated.
2. CMV also produces an encephalitis, similar to HIV dementia, that presents as a subacute decline in memory and cognition over 2-4 weeks, with periventricular changes on MRI.
3. The CSF CMV polymerase chain reaction test will be positive.
4. Ganciclovir (Cytovene) is a suppressive agent for CMV retinitis, but it has not proven effective for encephalitis. Foscarnet is an alternative IV antiviral agent that is used after ganciclovir fails.

F. Cerebral Toxoplasmosis

1. Toxoplasmosis encephalitis is a reactivated disease that occurs at CD4 counts less than $100/\mu\text{L}$ in about 30% of individuals with serological evidence of prior exposure (positive antibody). *Toxoplasma gondii* is an obligate intracellular protozoan, and infection causes brain abscesses.
2. Toxoplasmosis occurs in 5-10% of patients with AIDS, presenting with fever, altered mentation, seizures, and focal neurologic signs that develop subacutely over a few days. It is the most common cause of isolated CNS disease in HIV-infected patients.
3. Imaging studies demonstrate multiple, contrast-enhancing, mass lesions ("ring lesions"), but the radiologic appearance is not specific for toxoplasmosis and can be mimicked by lymphoma or other causes of abscesses.
4. Lesions are often multifocal and scattered throughout the cerebral hemispheres, though they have a predilection for the basal ganglia.
5. MRI is more sensitive than CT at detecting the multiple and characteristically ring-enhancing lesions.
6. Serologic testing of blood for toxoplasmosis is of diagnostic help in distinguishing among causes of focal brain lesions. Patients with cerebral toxoplasmosis rarely have negative serum IgG antibody titers. A negative titer in a patient with an intracranial mass lesion suggests an alternative diagnosis. Only about 1-2% of patients with proven toxoplasmosis have undetectable

Toxoplasma IgG.

7. It is common practice, with evidence pointing to toxoplasmosis, to initiate toxoplasmosis therapy as a diagnostic-therapeutic strategy. Also see "Toxoplasmosis," page 100.
8. **Treatment of Toxoplasmosis Encephalitis**
 - a. Antimicrobial therapy consists of pyrimethamine (Daraprim), 150 mg load, then 75 mg daily, with sulfadiazine, 1.5 mg four times daily.
 - b. Corticosteroids should be avoided if possible.
 - c. Clinical response, including a reduction in headache and fever, by 7 days supports the presumptive diagnosis of toxoplasmosis encephalitis. If clinical improvement does not occur within 10 days or if clinical deterioration has occurred by day 3, toxoplasmosis is unlikely, and a brain biopsy should be considered.
 - d. For patients with a good response, a repeat CT or MRI in four weeks will confirm reduction in the size of the lesions.
 - e. Lifelong suppressive therapy is necessary.

G. Primary Central Nervous System Lymphoma

1. About 4% of patients with AIDS develop a primary CNS lymphoma. It is the second most common cause of isolated CNS disease in HIV-infected patients.
2. The typical presentation is of slowly progressive neurologic deterioration over weeks with focal signs and seizures, leading to death within 3 months. Constitutional symptoms of fever and malaise are characteristically absent.
3. Lymphoma presents radiographically as a focal brain lesion, sometimes occurring as one or a few lesions, with variable surrounding enhancement and edema. Lymphoma tends to be diffusely enhancing, whereas toxoplasmosis lesions tend to be "ring" enhancing.
4. Because of the difficulty in distinguishing toxoplasmosis from lymphoma, empiric toxoplasmosis therapy is usually initiated for most patients with an intracranial mass lesion, particularly if it is enhancing.
5. If no response to toxoplasmosis therapy occurs, brain biopsy should be considered to rule out CNS lymphoma.
6. CSF cytologic examination is not useful for the diagnosis of lymphoma, and lumbar puncture may be contraindicated because of the risk of herniation.
7. The lymphoma responds to whole-brain radiation; however, because of progression of systemic HIV disease, survival time is short (3 to 6 months).

H. Progressive Multifocal Leukoencephalopathy

1. PML develops in 4% of patients with AIDS. It is characterized by progressive accumulation of focal neurologic deficits over weeks. Constitutional symptoms such as fever or altered consciousness are notably absent.
2. PML is an opportunistic infection caused by reactivation of the human papovavirus, JC virus, that is a ubiquitous infection.
3. Imaging studies demonstrate multiple, asymmetric, nonenhancing lesions in the subcortical white matter, without mass effect. MRI lesions are white on T2 and black on T1. MRI is more sensitive than CT scan.

4. CSF is positive for JC virus polymerase chain reaction, but this test is not readily available.
5. Biopsy may be necessary to differentiate PML from cerebral toxoplasmosis, other opportunistic infections, or CNS lymphoma.
6. PML usually progresses inexorably to death over weeks, or at most a few months. Spontaneous remission has been clearly documented on rare occasions.
7. **Treatment:** Aggressive antiretroviral therapy to reverse HIV-related immunosuppression may sometimes provide remission. Cytosine arabinoside is experimental and may slow progression.

I. Neurosyphilis

1. While it is not strictly an opportunistic infection, the course of syphilis is accelerated by the disturbance in cellular immunity in HIV infection. The time course from primary to tertiary syphilis is shortened.
2. Serologic tests for syphilis are usually reliable for the diagnosis of syphilis.
3. When patients with syphilis have neurologic symptoms, the CSF should be examined. If the CSF VDRL test result is positive or the serum rapid plasma reagin is high ($>1:16$), treatment should be initiated with IV penicillin, 24 mU for 10 days, or procaine penicillin, 2.4 mU with probenecid for 10 days, followed by re-examination of the CSF 2 months after therapy.

References: See page 108.

Dermatologic Care of the HIV-Infected Patient

I. Clinical Evaluation of Cutaneous Disease

- A. The greater the degree of immunodepression in the HIV-infected patient, the greater the likelihood of an unusual presentation and/or disease course.
- B. **Early HIV disease (CD4 >400/ μ L)**
 - 1. Usually only skin disease typical of the risk factors for HIV disease are seen (e.g., genital HSV, genital warts).
 - 2. At this stage human papilloma virus (HPV) infection may be resistant to therapy.
 - 3. Kaposi's sarcoma may sometimes appear at this stage. Less commonly, thrush, oral hairy leukoplakia, and herpes zoster may develop.
- C. **Early Symptomatic Phase (CD4 200-400 cells/ μ L)**
 - 1. Disorders of subtle immune imbalance occur, including candidiasis, oral hairy leukoplakia, herpes zoster, psoriasis, seborrheic dermatitis, and atopic dermatitis.
 - 2. Response to treatment is usually normal at this stage.
- D. **Early Stage AIDS (CD4 less than 200 cells/ μ L)**
 - 1. Opportunistic infections may present on the skin (cryptococcosis, histoplasmosis), and skin infections become chronic (chronic herpes simplex).
 - 2. At this stage HIV specific inflammatory diseases also appear. Pruritus is very common with a CD4 less than 200 to 300.
 - 3. Drug reactions, insect bite hypersensitivity, and itchy folliculitis are all manifestations of the enhanced cutaneous reactivity seen in AIDS.
- E. **Late Stage AIDS (CD4 <50/ μ L):** Bizarre patterns of skin disease occur. Treatment failure, drug resistance and chronicity are characteristic of this stage of HIV disease.
- F. Biopsies and cultures are often required, and the pathologist should be alerted to the presence of HIV infection or AIDS because special stains are required to diagnose the infectious processes that occur.

II. Infectious Cutaneous Disorders

A. Bacterial Infections

- 1. *Staphylococcus aureus* is the most common cutaneous bacterial pathogen. *Staphylococcus aureus* infection may cause folliculitis, bullous impetigo, ecthyma, abscesses, hidradenitis suppurativa-like plaques, and cellulitis. *Staphylococcus aureus* is usually susceptible to trimethoprim/sulfamethoxazole; therefore, it is less common in patients on PCP prophylaxis.
- 2. **Folliculitis** is the most common form of staphylococcal infection seen in HIV-infected persons. The central trunk, groin and face are the most common sites of infection. The primary lesion is a follicular pustule, but lesions may be urticarial. Staphylococcal folliculitis of the trunk may cause severe pruritus with excoriation.
- 3. **Bullous impetigo** is quite common in the groin and axillae, and it presents as flaccid blisters which quickly rupture leaving small superficial erosions with a peripheral scale.
- 4. **Ecthyma** is a punched out ulcer with a sharp border. The base may be purulent, or may be covered with a thick, adherent crust. Lesions are most common on the lower legs, commonly overlying

a preexisting dermatitis.

5. Treatment of Cutaneous Staphylococcal Infections

- a. Patients with chills, fever, large abscesses or cellulitis should be admitted for intravenous therapy.
- b. Abscesses should be incised and drained.
- c. Localized infection may be treated on an outpatient basis with oral agents once cultures are taken. A penicillinase resistant penicillin (dicloxacillin) or first generation cephalosporin (cephalexin) is the first choice for therapy for 2-3 weeks.
- d. Since nasal carriage approaches 50% in these patients, rifampin 600 mg in a single daily dose for 5 days or intranasal mupirocin (Bactroban), may be added in refractory or relapsing cases.
- e. Cleansing with benzoyl peroxide washes or antibacterial soaps may be beneficial to prevent relapse.

6. Bacillary Angiomatosis

- a. Bacillary angiomatosis (BA) is an uncommon subacute to chronic bacterial infection seen most commonly in the setting of AIDS with a CD4 of less than 50.
- b. Bacillary angiomatosis results from infection with *Bartonella henselae* (the agent of cat-scratch disease) or *Bartonella quintana* (the agent of trench fever). These bacteria are extremely difficult to culture; therefore, the diagnosis is usually established by identifying the agent in biopsy of affected tissue.
- c. The skin lesions are the most frequent presentation and appear as either friable vascular papules, subcutaneous nodules, or cellulitic plaques. The lesions often have a collarette of scale at the base. They may occur anywhere on the skin and on mucosal surfaces, especially in the respiratory tract and conjunctiva.
- d. Visceral disease, with or without skin lesions, is common. Indicators of chronic infection such as fever, night sweats, anemia or an elevated sedimentation rate are often present. The major forms of visceral disease involve the liver and spleen, osteolytic bone lesions, lymphadenopathy, and bacteremia.
- e. Liver disease is the most common visceral disease and is characterized by hepatosplenomegaly, abdominal pain, and elevated liver function tests. Ultrasound may show echogenic lesions, and CT demonstrates heterogeneity of the liver parenchyma.
- f. Bone lesions occur in about 15% of patients and may appear up to a year before other organ involvement. They present as painful, osteolytic foci, most commonly of the long bones, especially the tibia. Subacute osteomyelitis in HIV-infected persons should be considered bacillary angiomatosis until proven otherwise.
- g. **Diagnosis**
 - (1) The diagnosis of bacillary angiomatosis should be entertained in any HIV-infected person with bacteremia and/or vascular lesions of the skin, viscera, or bone.
 - (2) *Bartonella* serology is very sensitive.
 - (3) A biopsy from any affected tissue should be performed.

h. Treatment of Bacillary Angiomatosis

- (1)** The treatment of choice is erythromycin orally at a dose of 500 mg four times daily. Doxycycline, 100 mg orally twice daily, has also been effective in patients intolerant of erythromycin.
- (2)** A minimum of 8 weeks of treatment is completed. Visceral disease is treated for 4 months. If treated adequately, patients usually do not relapse and chronic therapy is not required in most cases.

B. Viral Infections

1. Herpes Zoster

- a.** Herpes zoster occurs in up to 8% of HIV-infected persons, and it occurs relatively early in the course of HIV infection, with an average CD4 count of 315 cells/ μ L.
- b.** Zoster is characterized by disesthesia, followed by a rash that progresses from macular to vesicular lesions with crusting along cutaneous nerves.
- c.** Usually, the course of herpes zoster is uneventful, although persistent postherpetic neuralgia may occur. In patients with more advanced HIV disease, herpes zoster may be very painful, severe, and prolonged. Dissemination may occur, but is usually limited to skin.
- d.** Uncomplicated herpes zoster is treated with acyclovir, 800 mg PO five times daily for 7-10 days or until lesions resolve. Varicella or zoster in the ophthalmic distribution of the trigeminal nerve is treated with intravenous acyclovir (Zovirax), 10 mg/kg q8h for 1-2 weeks.
- e. Prophylaxis:** Varicella-zoster immune globulin is indicated for susceptible persons within 3 days of exposure to varicella or zoster.

2. Herpes Simplex

- a. Herpes Simplex Viruses (HSV)** types I and II are recurrent diseases in immunocompetent individuals. In HIV infection, the frequency and severity of lesions are increased. Both oral-labial and genital lesions become painful, fixed ulcerations.
- b.** Perianal and rectal outbreaks occur even in the absence of a history of anal intercourse. Perianal outbreaks are frequently unrecognized and passed off as hemorrhoids or fissures.
- c.** Severe rectal disease may result in proctitis with painful tenesmus to the point of incontinence and urinary retention caused by anal sphincter spasm.
- d.** Disseminated herpes simplex is rare in HIV disease.
- e.** Once the CD4 count is less than 200, herpetic lesions present as persistent nonhealing ulcers. Lesions are often secondarily infected.
- f.** A viral culture or fluorescent antibody examination may be used to confirm the clinical diagnosis. Biopsy of the edge of an ulcer may be necessary for recalcitrant disease.
- g. Treatment:** Acyclovir (Zovirax) 200-400 mg PO 5 times/day for 7-10 days or until response occurs. Dosage of up to 800 mg PO 5 times/day may be needed for resistant disease. Severe or disseminated infection is treated with acyclovir 5 mg/kg IV q8h.
- h.** Foscarnet is an alternative for resistant disease; 40 mg/kg IV q8h.

- i. **Secondary Prophylaxis:** Frequent recurrences may justify long-term suppression with acyclovir. Resistant HSV has emerged in patients with HIV under prolonged treatment; fortunately, the frequency of this complication has been low.
3. **Molluscum Contagiosum**
 - a. Molluscum contagiosum is extremely common in patients with AIDS.
 - b. Lesions appear as umbilicated, pearly 2-5 mm papules on the face, genital area, and scattered on the trunk. There is a predilection for lesions to occur on the eyelids. Lesions may number from one to hundreds.
 - c. Disseminated cryptococcosis and herpetic folliculitis may mimic molluscum contagiosum.
 - d. **Treatment:** Lesions are usually treated with curettage, cryotherapy with liquid nitrogen, or electrocautery. Complete eradication is extremely difficult. Use of a new or clean razor blade daily for shaving is recommended.

III. Hypersensitivity Disorders

A. Drug Reactions

1. 50% of persons treated with trimethoprim/sulfamethoxazole (TMP/SMZ) for *Pneumocystis pneumonia* will develop a widespread morbilliform eruption.
2. The rash may resolve with continued treatment, but often persists or progresses with continuation of the drug.
3. Therapy may be continued if symptoms are not severe and progression has not occurred.
4. Similar reactions are seen due to virtually all other medications, but seem to be most common to antibiotics, especially the penicillins, and sulfa drugs. Cutaneous reactions are unusual to acyclovir, AZT, DDI, and lamivudine (3TC). Fluconazole may cause dryness of the lips.
5. Desensitization is used for reinstitution of necessary medications if the drug reaction was mild.
6. In addition to morbilliform reactions, erythema multiforme, and fixed drug eruptions are seen with increased frequency. In some patients, erythema multiforme may be quite severe--Steven Johnson syndrome or toxic epidermal necrolysis. These severe reactions are most commonly due to sulfa drugs and anticonvulsants.

B. Scabies

1. Scabies, flea bites, and mosquito bites may all cause severe pruritus and eruptions in the setting of HIV disease.
2. The most common cause of insect bite reactions is scabies, and it should be considered as the cause of all rashes because most HIV-positive patients will get scabies.
3. Scabies eruptions present as non-follicular papules to cellulitic plaques with marked pruritus. The fingerwebs, genitalia, axillae, and feet should be carefully examined for lesions. When lesions are found in these areas, they should be scraped to search for scabietic mites.
4. **Scabies** is a common cause of lower leg pruritic papules, nodules, and blisters. Scabies may significantly exacerbate other chronic skin conditions including eczema and psoriasis.

5. Treatment of Scabies

- a. **Lindane (Kwell)** cream (CD4 >200 cells/ μ L) or **lotion or permethrin (Elimite) 5%** cream (CD4 <200 cells/ μ L) is applied to the whole body once for 12 hours and repeated in one week.
- b. Persons with more advanced HIV infection (with CD4 counts below 200) may fail lindane therapy. These patients need to be treated twice with permethrin, and atypical cases may require constant treatment for 36 weeks. Contacts should also be treated, and clothing should be washed in hot water.
- c. **Norwegian scabies** causes extensive, crusted scabies lesions and occurs in patients with advanced HIV disease. It is non-pruritic and mimics psoriasis. Treatment consists of removal of thick plaques with mineral oil and permethrin (Elimite) 1 day, Kwell the next, and 6% sulfur in petrolatum for 5 days, repeated for several weeks until the patient is cured. Norwegian scabies is extremely infectious, and the disease often spreads rapidly throughout the entire hospital ward.

C. Photosensitivity

1. HIV disease alone or medications taken by HIV-infected patients may lead to cutaneous eruptions, predominantly in sun-exposed areas (photodermatitis).
2. Eruptions initially may manifest as an enhanced sunburn, but may progress to pruritic scaly patches. Trimethoprim/sulfamethoxazole and dapsone are photosensitizing agents.
3. Eruptions are frequently excoriated, become thickened, and often cause hypo- or hyperpigmentation, especially in persons of color. With time the eruption may extend to unexposed skin.
4. **Management of Photodermatitis**
 - a. Discontinue potential photosensitizers (sulfa drugs, NSAID's).
 - b. Apply sunscreens, use hats and clothing, and avoid sun exposure.
 - c. Apply a medium to high potency topical steroid.
 - d. Potent antihistamines such as doxepin and oral corticosteroids may be needed.

D. Eosinophilic Folliculitis

1. Eosinophilic folliculitis is the most common non-staphylococcal folliculitis in HIV-infected persons. One in five HIV-positive patients with pruritus has eosinophilic folliculitis
2. This disorder is a chronic waxing and waning inflammatory process of the hair follicle with moderate to severe pruritus. The disorder is caused by a mite.
3. The disorder occurs in patients with CD4 counts near to or less than 200 cells/ μ L.
4. 90% of eosinophilic folliculitis lesions will appear down the midline of the back, or up into the back of the scalp. Lesions may be hyperpigmented in dark skinned people.
5. The primary lesion is an, up to 1 cm, edematous papule with a tiny central pustule. The lesions are scattered on the upper trunk, head (especially forehead), neck, and proximal upper extremities.
6. **Diagnosis**
 - a. Lesions should be cultured to rule out bacterial folliculitis, which is more likely to persist rather than wax and wane.

Cultures for bacteria are uniformly negative in eosinophilic folliculitis, and the patients do not respond to antibiotics effective against *S. aureus*.

- b. Skin biopsy of a lesion reveals inflammation containing significant numbers of eosinophils surrounding and involving the hair follicle.

7. Treatment

- a. Itraconazole in a dose of 200 mg to 400 mg daily provides improvement in 70% of patients. If there is no response after 2 weeks, the dose is doubled.
- b. Topical therapy chronically, qOD with 5% permethrin cream or sulfacet R may lead to a more sustained remission.
- c. Phototherapy with UVB may be beneficial.
- d. Antipruritics such as diphenhydramine or hydroxyzine may reduce scratching.

E. Papulosquamous Disorders

- 1. Three dermatologic disorders characterized by scaling patches and plaques are seen commonly in HIV-infected persons--seborrheic dermatitis, psoriasis, and Reiter's syndrome.

2. Seborrheic Dermatitis

- a. Up to 80% or more of HIV/AIDS patients will have this disorder at some point, especially as the CD4 cell count drops, most persons with symptomatic HIV disease will have this disorder.
- b. Lesions are usually located on the face, eyebrows, retroauricular areas, nasolabial folds, scalp, chest, back and groin. The lesions are mildly erythematous with a yellowish greasy scale. When limited to the face, lesions are usually asymptomatic, but scalp and trunk lesions are often pruritic.
- c. Scabies often mimics seborrheic dermatitis, and scabies should always be excluded in cases of seborrheic dermatitis.
- d. **Therapy**

(1) Scalp therapy includes a dandruff shampoo containing selenium sulfide (Selsun), zinc pyrithione (Head and Shoulders), or sulfur and salicylic acid (Sebulex). A medium potency steroid solution (triamcinolone 0.1%) is added.

(2) For facial, trunk and groin lesions a topical imidazole cream [ketoconazole (Nizoral) 2%, clotrimazole 1%], plus a low potency topical steroid (hydrocortisone 1-2.5%) is applied twice daily. For refractory trunk lesions, the strength of the topical steroid may be increased.

(3) Severe cases may require ketoconazole 200-400 mg po qd for 3-4 weeks. Maintenance therapy with hydrocortisone cream 1% and ketoconazole cream 2% bid is used indefinitely.

3. Psoriasis

- a. The initial lesions frequently begin like seborrheic dermatitis, but extend to the axillae and groin, and finally involve the elbows, knees and lumbosacral areas.
- b. The lesions of psoriasis and seborrheic dermatitis in the axillae and groin are identical. When psoriasis involves the trunk, it tends to form more fixed, less easily treatable lesions with a thicker silvery scale.

pustules that evolve into a hyperkeratotic papules. Arthritis may be present with psoriasis alone or as a part of Reiter's syndrome.

d. Treatment of Psoriasis

- (1)** Mild to moderate psoriasis is managed with topical steroids (triamcinolone 0.1% ointment bid) and 2% crude coal tar.
- (2)** Patients with severe psoriasis and HIV disease may note a significant improvement of their skin lesions with zidovudine therapy.
- (3)** Etretinate, a vitamin A analog, is often beneficial. It is nonimmunosuppressive and well tolerated.

Assessment of Fever in the HIV-Infected Patient

Infection is the most common cause of fever in AIDS patients. Diagnostic attention should first be directed to the possibility of infection or drug-induced fever.

I. Clinical Evaluation of Fever in HIV-Infected Patients

- A. Protracted unexplained fever is usually caused by either *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex infection, tuberculosis, sinusitis, cryptococcosis, or non-Hodgkin's lymphoma.
- B. Protracted fever can be the sole presenting feature in severely immunocompromised patients with *P carinii* or cryptococcal meningitis.
- C. In patients receiving prophylactic trimethoprim-sulfamethoxazole, *P carinii* pneumonia, toxoplasmic encephalitis, and salmonella bacteremia are less likely to occur.
- D. In early-stage patients (CD4 counts $>200/\mu\text{L}$), fevers may be a manifestation of HIV itself and are typically low-grade.
- E. In patients with later-stage disease who develop significant and persistent fevers, *Mycobacterium avium* complex (MAC) infection and lymphoma are common.
- F. Cryptococcal meningitis is a consideration in patients with fever accompanied by acute or chronic headache or changes in mental status.
- G. If there are no focal neurologic, respiratory, or GI findings, the possibility of medication side effects, especially with sulfa drugs, should be considered.

II. History

- A. Information from the patient's history may include residence in an area endemic for histoplasmosis or tuberculosis, or it may include failure to comply with anti-*Pneumocystis* prophylaxis.
- B. Homosexual and bisexual men who do not engage in "safe sex" practices are predisposed to *Salmonella* bacteremia and to proctitis caused by herpes simplex virus, *Treponema pallidum* or *Chlamydia trachomatis* or to proctocolitis caused by *Shigella* or *Campylobacter* species, *C trachomatis*, *Entamoeba histolytica* or *Clostridium difficile*.
- C. Fever and inguinal adenopathy suggests infection caused by herpes simplex virus, *C trachomatis*, or *T pallidum*.
- D. **Drug-induced Fever**
 1. Drug-induced fever is commonly attributed to antimicrobials (TMP-SMX, clindamycin, dapsone, amphotericin B), antivirals (zidovudine, ganciclovir, interferon), isoniazid, and rifampin.
 2. When there is no readily identifiable explanation for fever, discontinuation of recently initiated drugs should be attempted.
- E. **Primary HIV Infection**
 1. Fever is the most common manifestation of symptomatic primary HIV infection. Additional findings include malaise, sweats, weight loss, arthralgia, myalgia, headache, pharyngitis, lymphadenopathy, and skin rash.
 2. The symptomatic primary infection resolves spontaneously, usually within 2 to 3 weeks.

III. Diagnostic Approach to Fever in the HIV-Infected Patient

A. Approach to the Febrile Patient with a CD4+ count above 200 cells/ μ L

1. Traditional bacterial infections (bronchitis, sinusitis, pneumonitis, bacteremia, pelvic inflammatory disease, pyelonephritis, cellulitis), viral respiratory infections, and tuberculosis (pulmonary, extrapulmonary, or combined) are the common causes of fever.
2. *P. carinii* pneumonia occasionally develops in HIV-infected patients with CD4+ counts above 200/ μ L; however, other opportunistic infections (cryptococcal meningitis, disseminated histoplasmosis, *M. avium* complex infection, toxoplasma encephalitis, cytomegalovirus) almost never occur at this stage.
3. Evaluation of these patients should include a thorough history and physical examination, a complete blood cell count, chest x-ray, urinalysis, blood cultures, and liver enzyme tests (alcoholic, drug-induced, or viral hepatitis), VDRL, and amylase.
 - a. A tuberculin skin test should be done if PPD status is unknown or if a previous test was negative.
 - b. Blood cultures for fungi and mycobacterium and a cryptococcal antigen test should be considered.
4. Patients who appear seriously ill, who have significant leukopenia (white blood cell count < 500/ μ L) are candidates for hospitalization and empirical antibiotics.
5. Medications that are not considered absolutely essential should be discontinued in order to determine if the fever is drug-induced.
6. When fever persists and cannot be explained (there are no focal symptoms such as cough, shortness of breath, headache, confusion, abdominal pain, or diarrhea), recent use of antibiotics should be determined, and sinus films obtained.

B. If the patient is an injecting drug user, persistent fever may be caused by culture-negative endocarditis, osteomyelitis, or occult tuberculosis.

C. HIV-Infected Patients with CD4+ Counts Below 200/ μ L

1. Disorders previously mentioned should be considered plus neoplasms (non-Hodgkin's lymphoma) and opportunistic infections.
2. Opportunistic infections include *P. carinii* pneumonia or disseminated disease, disseminated infection with *Histoplasma capsulatum*, cryptococcal meningitis or disseminated disease, *Toxoplasma gondii* encephalitis or disseminated disease, disseminated mycobacterial (*M. avium* complex, *M. genavense*, *M. chelonae*) disease, *Bartonella henselae* infection, and *Helicobacter cinaedi* bacteremia.
3. A thorough investigation most often uncovers either *Pneumocystis carinii* pneumonia (particularly if the patient has not been compliant with TMP-SMX prophylaxis), disseminated *M. avium* complex or *M. tuberculosis* infection, or non-Hodgkin's lymphoma.
4. In patients with symptomatic *P. carinii* pneumonia, 20% of chest films fail to reveal a typical infiltrate.
5. Computed tomography is used for investigating symptoms attributable to central nervous system disease and for assessing patients for evidence of sinusitis. However, magnetic resonance imaging has greater sensitivity in detecting cranial neurologic illness.
6. Computed tomography is highly useful in identifying specific occult abdominal diseases that can produce fever, including *M. avium* complex infection, tuberculosis, cytomegalovirus colitis, hepatic abscesses, hepatic masses, infectious cholangitis, visceral Kaposi's

sarcoma, and non-Hodgkin's lymphoma.

7. Bone marrow aspiration for examination and culture is a valuable diagnostic procedure for revealing opportunistic mycobacterial and fungal infections in HIV-infected patients with CD4+ counts below 200/ μ L.
8. Liver biopsy may provided a diagnosis of mycobacterial and cytomegalovirus infection in profoundly immunosuppressed AIDS patients with unexplained fever and abnormal results on liver enzyme tests.

Diagnostic Studies for Fever in HIV-Infected Patients

Cause	Study
Pneumocystis carinii pneumonia	Bronchoalveolar lavage examination
Disseminated Histoplasma capsulatum	Blood culture (lysis-centrifugation technique) Bone marrow examination Antigen determination
Cryptococcal meningitis or disseminated disease	CSF, urine, blood cultures Blood, CSF antigen testing India ink preparation of CSF Tissue stains, cultures
Disseminated Toxoplasma gondii	Tissue stains PCR on blood samples Isolation of organism from CSF, blood, bronchoalveolar fluid
Disseminated mycobacterial disease	Blood culture Bone marrow examination, liver biopsy
Bartonella henselae	Blood or tissue culture
Helicobacter cinaedi	Blood culture

D. Tuberculosis

1. HIV-infected patients who are injecting drugs, who have immigrated from countries where tuberculosis is endemic, or who are in close contact with infected patients are predisposed to tuberculosis.
2. HIV infection increases the risk of reactivating a latent infection.
3. Although tuberculosis is primarily a pulmonary infection, HIV-infected patients with tuberculosis tend to demonstrate extrapulmonary disease.
4. Manifestations of pulmonary and extrapulmonary disease include fever, night sweats, weight loss, anorexia, chills, cough, headache, meningismus, hepatosplenomegaly, and lymphadenopathy.
5. To establish a diagnosis of tuberculosis, multiple sputum, stool, and urine specimens should be processed for acid-fast stains and cul-

tures. In patients with advanced immunosuppression, *M. tuberculosis* may sometimes be isolated from blood. Lumbar puncture, bone marrow aspiration, liver biopsy, and bronchoscopy may also be necessary.

6. Empirical antituberculous therapy can be prescribed while awaiting the results of smears and cultures.

E. Mycobacterium Avium Complex Infection

1. Mycobacterial infections often manifest as persistent occult fever in HIV-infected patients. Mycobacterium avium complex usually causes disseminated infection. Clinical features of disseminated M avium complex infection include anorexia, weight loss, fever, night sweats, weakness, and diarrhea.
2. The risk for Mycobacterium avium complex (MAC) develops late in disease, with most cases diagnosed at CD4 counts under $50/\mu\text{L}$. A fever without clinical source in patients with such counts is most commonly due to MAC bacteremia.
3. Physical examination often will reveal hepatosplenomegaly along with cachexia. Common laboratory abnormalities include anemia, leukopenia, and liver enzyme abnormalities.
4. The diagnosis can be established easily by specific mycobacterial blood culture employing the lysis centrifugation technique. Two or three blood cultures drawn over a few days is generally sufficient to recover the organism.
5. The organism also can be cultured from a biopsy specimen of liver, bone marrow, or lymph node. The presence of Mycobacterium avium complex in stool or sputum is not diagnostic of invasive infection, but should raise the suspicion of active or impending disease.
6. Treatment is usually based upon isolation of MAC, although, because of the time delay, patients with no other cause of fever and low CD4 counts may be started on a therapeutic/diagnostic trial looking for defervescence.
7. Treatment requires multiple antibiotics employing ethambutol and a second-generation macrolide (clarithromycin or azithromycin). The addition of a third antibiotic (rifabutin) is common. Therapy should be provided indefinitely.

F. Histoplasmosis

1. This infection is a disseminated disease characterized by persistent fever and weight loss, often unassociated with respiratory symptoms.
2. The disease develops in patients who reside in endemic areas (Ohio, Mississippi River Valley, Indianapolis), or who have immigrated from endemic areas (Puerto Rico, Colombia, Dominican Republic), or who work in construction, or who have contact with loci contaminated with *H. capsulatum* (in caves, farms, bird roost sites).
3. Disseminated histoplasmosis occasionally presents as fever of unknown origin; in such cases, pulmonary symptoms may be absent and chest films may be normal.
4. **Diagnostic studies** include serologic tests for antigen and antibody, isolation of the organism in body fluids and tissues, and recovery of the organism from blood (lysis-centrifugation technique), bone marrow, cerebrospinal fluid, or bronchoalveolar lavage fluid.

G. Non-Hodgkin's Lymphoma

1. Systemic non-Hodgkin's lymphoma can cause fever accompanied by night sweats, fatigue, and weight loss. Systemic lymphomas usually develop in HIV-infected patients with CD4+ counts less than 200/ μ L.
2. Systemic lymphomas are characterized by widespread extranodal dissemination (to bone marrow, liver, meninges, and gastrointestinal tract) and by appearance at unusual sites (testes, parotid gland, gingiva, appendix).
3. Abnormalities that heighten suspicion for non-Hodgkin's lymphoma include asymmetric or rapidly progressive lymphadenopathy; hepatomegaly, splenomegaly, unexplained gastrointestinal symptoms; obstructive biliary disease, hilar adenopathy, an abdominal mass, elevated serum alkaline phosphatase level, a markedly abnormal serum lactate dehydrogenase level, or a sudden decrease in all peripheral blood cell lines.
4. Treatment with multi-agent chemotherapy may extend survival, but the overall prognosis is poor.

References: See page 108.

HIV-Associated Psychiatric Disorders

I. Depression in HIV-Infected Patients

- A. The greatest risk for depression occurs in patients who have had a prior episode of depression.
- B. The incidence of depression in HIV infection is 7-10%, and the risk is particularly high immediately before and after HIV testing. A patient's risk of suicide is elevated in the immediate weeks or months after HIV antibody testing.
- C. Depression may also occur when a seropositive person first develops symptoms.
- D. Medications commonly taken by AIDS patients, including AZT, acyclovir, interferon INH, sulfonamides and narcotics, can cause neuropsychiatric problems such as depression or delirium.
- E. Patients with depression should be screened carefully for substance use because substance use or withdrawal can cause depression and psychomotor agitation.
- F. Chronic pain can also cause depression and anxiety. Chronic headache due to HIV encephalitis, or chronic extremity pain due to peripheral neuropathy are common causes of pain. Optimization of pain control may bring improvement in the psychiatric disease.
- G. Some symptoms of depression, such as fatigue, are common manifestations of HIV infection itself.

H. Diagnostic Criteria for Major Depressive Episode

At least one of the first two, for two weeks or more.

Anhedonia

Depressed mood

Difficulty in thinking or concentrating

Fatigue or anergy

Feelings of guilt or worthlessness

Psychomotor agitation or slowing

Significant and unintentional change in weight

Sleep disturbances

Suicidal ideation

- I. **Diagnostic Evaluation:** Imaging studies and screening for cryptococcal disease and syphilis with serological testing should be undertaken if symptoms suggest the presence of a new CNS disease (headache, focal neurological symptoms, signs of frontal lobe disease). Further evaluation is also necessary for patients with refractory depression.

J. Treatment of Depression

- 1. Psychiatric referral of the depressed patient may be appropriate if suicidal ideation is strong or if additional psychiatric problems or substance abuse complicate treatment.
- 2. The choice of antidepressant depends largely on what adverse effects the person is likely to tolerate.
- 3. **Tricyclic Agents**
 - a. Desipramine, which is the least sedating TCA, and nortriptyline, which is the least anticholinergic TCA, are useful agents because they have minimal side effects.
 - b. A tricyclic agent such as amitriptyline (Elavil) may be helpful for patients who have difficulty sleeping, although anticholinergic effects can be troublesome.
 - c. Many HIV patients have dermatitis and pruritus, and these

patients can benefit from an antidepressant that also has antihistaminic effects. Doxepin is a sedating TCA that has substantial antihistamine effects and can be very helpful for patients with pruritus that interferes with sleep.

- d. The tricyclics are useful in treating the chronic pain of peripheral neuropathy, which is a common side effect of some antiretroviral agents.
- e. If the patient is showing a good clinical response and has no evidence of medication side effects, obtaining drug levels is usually not necessary.
- f. Because TCAs can cause conduction defects, a baseline EKG should be obtained in patients older than 45 or in any patient with cardiac disease.
- g. Only small quantities of tricyclics should be prescribed at one time if the patient is a suicide risk because the average 7-10 day supply of a tricyclic antidepressant may be a lethal dose.

4. Selective Serotonin Reuptake Inhibitors

- a. The SSRIs include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) and venlafaxine-HCl (Effexor). They all share the properties of being well tolerated by most patients, with their initial side effects of hyperactivity, insomnia, nausea and headache usually subsiding within two to three weeks. In addition, their dosing is quite simple since the initial dose is often an effective therapeutic dose.
 - b. The selective serotonin reuptake inhibitors (SSRIs), because of their slight stimulant effects, are a good choice for patients who are fatigued or cognitively impaired. However, these agents have a high incidence of sexual dysfunction (10-20%).
 - c. SSRI's are preferable in a potentially suicidal patient because they have less overdose potential.
5. Bupropion (Wellbutrin) shares the advantage of being safer in overdose and of being free of anticholinergic side effects. Its disadvantages are that it must be taken two to three times a day, and that it has been noted to increase seizures in patients who have unstable seizure disorders. It is especially useful for patients who are unable to tolerate SSRIs due to sexual dysfunction problems. Like the SSRIs, bupropion can cause hyperstimulation symptoms during the first few weeks of therapy.
6. Many AIDS patients are highly sensitive to the effects of drugs that act on the CNS, and lower than usual dosages are used initially.
- a. In patients who are otherwise not medically ill and appear to have normal hepatic and renal function, standard initial dosing of a tetracyclic begins at 50 mg, gradually increasing to a therapeutic dose in the 100 mg to 200 mg range.
 - b. If the stimulant effect of the SSRIs is undesirable, these drugs should be started at lower dosages. Fluoxetine (Prozac) 20-mg capsules can be halved by dissolving the capsule in a cup of juice and drinking half the juice one day and the other half the next. The drug is also available in liquid form.
7. Depression associated with fatigue and malaise may respond to methylphenidate (Ritalin), starting with 5 mg twice a day; there is a risk of addiction and seizures. Dexedrine and androgens have also been used.

Antidepressants Used for HIV-Infected Patients

Name (Trade name)	Advantages	Disadvantages	Dosage Range and Comments
Tricyclic Antidepressants			
Amitriptyline (Elavil)	Useful for patients with insomnia; drug levels obtainable	Significant anticholinergic effects (dry mouth, constipation), antihistaminic (very sedating); dangerous in overdose	Also useful for chronic pain palliation, migraine prophylaxis, neuropathic pain; begin at 25-50 mg, increase by 25 mg q3days, up to 150-200 mg qhs
Desipramine (Norpramin)	Least sedating TCA; good choice for treating peripheral neuropathy; drug levels obtainable	Dangerous in overdose	Begin at 25-50 mg, increase by 25 mg q3days, up to 150-200 mg qhs
Nortriptyline (Pamelor)	Least anticholinergic TCA, established efficacy in neuropathic pain palliation; drug levels obtainable	Same as above	Begin at 25-50 mg, increase by 25 mg q3days, up to 150-200 mg qhs
Doxepin (Sinequan)	an excellent antihistamine	Very sedating	10-25 mg qhs-bid; 150-300 mg/d
Trazodone (Desyrel)	Very sedating - can use in low doses as a sleep agent	Very sedating - Often cause a.m. sedation; priapism occurs in 1/7,000	Often used with other antidepressants to treat sleep disturbance (25 - 50 mg qhs)
Selective Serotonin Reuptake Inhibitors			
Fluoxetine (Prozac)	Side effects usually limited to nausea, headache, agitation/insomnia, which resolve after 2 weeks; safe in overdose	Sexual dysfunction (20%). May cause tremor that subsides after 3 - 6 months.	Begin at 10 mg PO qAM with food x 2 - 4 days, then 20 mg/day; 20-80 mg/d
Sertraline (Zoloft)	Same as fluoxetine	Same as fluoxetine; occasionally causes diarrhea	Begin at 25 mg qAM x 2-4 days, then 50 mg per day. Maximal dose 200 mg/day.

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Paroxetine (Paxil)	Same as fluoxetine/sertraline	Same as fluoxetine	Begin at 10 mg qAM x 2-4 days, then 20 mg/day. Maximal dose 50 mg/day. Take qhs if daytime drowsiness occurs
Venlafaxine (Effexor)	Raises CNS levels of both serotonin and norepinephrine; well-tolerated first-line agent and useful in patients refractory to other antidepressants. Safe in overdose	Initial stimulant side effects	25-100 mg PO bid; begin at 25-37.5 mg bid
Atypical Agent			
Bupropion (Wellbutrin)	Usually does not cause sexual dysfunction	Contraindicated in unstable seizure disorders; tid dosing may compromise compliance	75-100 mg PO tid; begin at 75 mg bid. then increase to tid; can switch to bid after 2-3 weeks.

II. Anxiety and Panic Disorder

- A. HIV-positive patients commonly experience chronic anxiety that can be extremely disabling.
- B. Symptoms of anxiety include trouble falling asleep, impaired concentration or memory, fatigue and psychomotor agitation.
- C. Medications that may cause anxiety include corticosteroids, nonsteroidal anti-inflammatory drugs, and high-dose sulfonamide therapy.
- D. Anxiety also can be caused by substance use withdrawal. All patients with anxiety should be screened for substance use.
- E. Panic attacks are characterized by discrete intense episodes of anxiety that include physical symptoms such as dizziness, chest pain, shortness of breath, paresthesias of the fingers, toes and lips, and a sense of impending doom. Panic attacks can mimic neurologic and cardiopulmonary syndromes.
- F. **Treatment of Panic Attacks**
 1. In patients who have rare, situationally prompted panic attacks (e.g., before medical appointments), a short-acting prophylactic anxiolytic such as lorazepam (Ativan) or alprazolam (Xanax) may be quite effective.
 2. In patients who have frequent or chronic panic attacks, long-term treatment with an antidepressant for preventative purposes with supplementary short-acting anxiolytics for breakthrough symptoms is effective.
 3. TCAs are the mainstay of treatment for prevention of panic disorder.

G. Treatment of Chronic Anxiety

1. In episodic anxiety, short-acting anxiolytics are used. These include lorazepam (Ativan) and alprazolam (Xanax).
2. In chronic anxiety, long acting anxiolytics such as clonazepam (Klonopin) are used.
3. All patients receiving around-the-clock anxiolytics should be cautioned about the risk of sedative withdrawal. If the drug is to be discontinued, the dosage should be gradually tapered to avoid withdrawal symptoms.
4. Chronic anxiety also can be treated with buspirone (BuSpar), a non-addicting, non-sedating anxiolytic that may palliate chronic anxiety. At least two weeks is required to show efficacy; therefore, it is not useful for acute anxiety.

Treatment of Anxiety

Short and Rapid Acting Agents	
Alprazolam (Xanax) 0.25-2 mg PO q8h prn	Useful for situational or sporadic anxiety, or for breakthrough symptoms in panic disorder
Lorazepam (Ativan) 0.5-2 mg PO q8h prn	Useful for situational or sporadic anxiety, or for breakthrough symptoms in panic disorder
Long-acting Agents	
Clonazepam (Klonopin) 0.5-2 mg PO bid	Useful for generalized anxiety disorder (GAD), should be taken around-the-clock, not prn
Buspirone (BuSpar) 10-15 mg PO tid	Useful for generalized anxiety disorder; should be taken around-the-clock, not prn; slow onset of action (2-3 wks); nonsedating and non-addictive

III. Delirium

- A.** Delirium is a life-threatening complication of many medical diseases including HIV disease. In HIV disease, delirium can be caused by central nervous system opportunistic infections, non-central nervous system systemic illnesses, medication side effects, and organic brain disease.
- B.** Causes of delirium noted in the medically ill HIV-positive population include pentamidine-associated hypoglycemia and hypotension, hyperkalemia secondary to high-dose TMP/SMZ therapy, electrolyte disorders specifically due to amphotericin or foscarnet, hyponatremia due to SIADH or hypotonic fluid administration, hypoxemia due to respiratory illness.
- C.** Drugs that may cause delirium include corticosteroid-induced agitation and delirium caused by metoclopramide (Reglan), anticonvulsants, and ciprofloxacin. Delirium may be secondary to acute disinhibitory or withdrawal states from prescribed or recreational drugs.
- D.** Primary CNS disease should be ruled out with a lumbar puncture and/or CT scan.
- E. Treatment of Delirium**
 1. Delirious patients should be provided orientation information

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regularly and their sleep cycle should be disrupted as infrequently as possible (milieu management).

2. Agitation is treated with mid-potency neuroleptics such as Trilafon and/or intravenous short-acting anxiolytics such as lorazepam.
3. High-potency neuroleptics such as haloperidol (Haldol) have been noted to cause neuroleptic malignant syndrome and have an increased frequency of extrapyramidal syndromes in people with HIV disease.
4. Low-potency neuroleptics such as thioridazine (Mellaril) often cause undue confusion or sedation.

IV. Mania

- A. Mania is a disorder of mood characterized by persistently grandiose or irritable moods, decreased need for sleep, psychomotor agitation, inflated self esteem, and pursuit of pleasurable activities with impaired judgment. Severe mania may be difficult to distinguish from a psychotic disorder.
- B. Mania is commonly seen late in HIV disease, as a complication of organic brain disease, and it commonly complicates high-dose steroid use (for PCP).
- C. **Treatment of Mania**
 1. Initial stabilization is accomplished with mid-potency neuroleptics (e.g., Trilafon); steroids are tapered and discontinued or other contributing medications are discontinued.
 2. Lithium often is not appropriate for use in persons with AIDS because patients with advanced AIDS are prone to dehydration through diarrhea and vomiting, and to renal disorders because of the frequent use of potentially nephrotoxic drugs.
 3. Trilafon with or without concomitant lorazepam therapy is effective for initial stabilization, followed by either valproate or carbamazepine therapy for chronic mood stabilization.
 4. Depakote is usually given as an initial dosage of 250 mg three times a day, but higher doses (1000-1250 mg/d) may be required for mood stabilization.
 5. Carbamazepine (Tegretol) also may be useful, but may cause bone marrow suppression in patients with HIV disease who are already receiving marrow suppressive agents.

V. Psychosis

- A. HIV-positive patients may exhibit symptoms of psychosis that may include hallucinations, delusions, flight of ideas, and paranoid delusions.
- B. Central nervous system disease should be ruled out.
- C. Drug effects should be excluded, including corticosteroid-induced agitation and psychosis caused by metoclopramide (Reglan) or anticonvulsants. Psychosis may be secondary to acute disinhibitory or withdrawal states from prescribed or recreational drugs.
- D. **Treatment of Psychosis**
 1. Because of the risk of neuroleptic malignant syndrome and increased frequency and severity of extrapyramidal symptoms seen with high-potency neuroleptic medicines in advanced HIV disease, mid potency neuroleptic medicines such as Trilafon are generally the best treatment for HIV-associated psychosis.

2. Low-potency neuroleptics such as Thorazine and Mellaril often cause intolerable sedation.

References: See page 108.

HIV-Related Wasting Syndrome

Weight loss is a very common feature of late-stage HIV infection, and the HIV wasting syndrome is a frequent contributor to the demise of patients with AIDS.

HIV wasting syndrome ranks as the second most frequent diagnosis during the in six months prior to death. It is the first progression of disease event in 10-11% of HIV-infected patients. Malnutrition can have devastating clinical implications on HIV-related immune suppression.

I. Clinical Evaluation

- A. Anorexia is usually severe, and diarrhea frequently accelerates the HIV wasting. Wasting accompanied by fever and night sweats may signal *Mycobacterium avium* complex infection.
- B. The CDC definition of wasting syndrome consists of loss of >10% of body weight plus either diarrhea, fatigue or fever.
- C. Loss of >30% of body cell mass is as poor a prognostic indicator as a CD4 count of less than 50/ μ L.
- D. The etiology of HIV-related wasting is frequently multifactorial.
 - 1. Decreased oral intake may be secondary to CNS processes, local GI effects, or anorexia that is also multifactorial in nature.
 - 2. Malabsorption may contribute to the wasting process.
 - 3. Cytokines, particularly tumor necrosis factor-alpha (cachectin), have been implicated.
 - 4. Endocrine abnormalities may be involved.

II. Treatment of HIV-Related Wasting Syndrome

- A. Control of diarrhea will usually reduce weight loss. The underlying etiology should be treated when possible. Depression, opportunistic infections and malignancies should be diagnosed and treated.
- B. Adequate exercise should be encouraged.
- C. Nutritional supplementation is best used prior to significant weight loss.
 - 1. Nutritional supplements taken by the enteral route are preferable when gastrointestinal function is intact.
 - 2. Total parenteral nutrition has been demonstrated to produce weight gain; however, weight gain is mainly due to an increase in fat.
- D. **Appetite Stimulating Agents**
 - 1. **Dronabinol (Marinol)**, a cannabinoid, has been shown to increase appetite and reduce nausea, but no significant weight gain was appreciated; 2.5 mg PO bid before lunch and dinner; up to 10 mg PO bid.
 - 2. **Megestrol acetate (Megace)**, a progestational hormone, also has appetite stimulating effects which produce some weight gain. An eight pound weight gain was appreciated in a 12 week trial at 800 mg daily; however, weight gain was predominantly fat.
- E. **Anabolic Steroids**
 - 1. **Testosterone** is useful for wasting syndrome only if HIV-related hypogonadism exists.
 - a. The incidence of HIV-related hypogonadism increases with advanced disease states.
 - b. Oral agents are unreliable due to a first pass effect that metabolizes the hormone, and they pose a risk of hepatotoxicity.

- c. Testosterone enanthate and testosterone propionate are used at dosages of 200-400 mg IM two times a month.
 - d. Transdermal systems require nearly constant wearing of the patch.
2. Nandrolone decanoate intramuscular injections and oral oxandrolone are two additional anabolic steroids now entering clinical trials for HIV-related wasting following encouraging preliminary evaluations.
- F. Human growth hormone** has been demonstrated to produce a clear gain in lean body mass in a placebo-controlled trial; however, high cost prevents common usage.
- G. Inhibitors of Tumor Necrosis Factor-alpha.**
- 1. Thalidomide is widely used by patients as a possible wasting therapy. A recent controlled trial demonstrated marked efficacy against oral aphthous ulcers.
 - 2. Access via buyer's clubs is common.

References: See page 108.

HIV Infection in Women

The incidence of AIDS is increasing faster in women than in men. HIV infection is the third leading cause of death among women aged 25-40 in the United States. It is the leading cause of death among black women and the fifth leading cause for white women.

I. Epidemiology

- A. Twelve percent of AIDS cases occur in women nationally, of whom 80% are of reproductive age.
- B. Most cases of AIDS in women can be attributed directly or indirectly to drug use. In the early years of the epidemic, the majority of women diagnosed with AIDS were intravenous drug users. Over time, the proportion of women infected through heterosexual contact has increased, accounting for 38% of women.
- C. Among women infected heterosexually, a large proportion contracted HIV from a sex partner who was an IV drug user. IV drug use remains the predominant mode of transmission among women reported with AIDS in the Northeast, but heterosexual contact accounts for more cases in the Midwest, South, and West.
- D. Five instances of female-to-female transmission of HIV infection have been reported in the medical literature, suggesting that the risk of female-to-female transmission is very low.

II. HIV Disease Course in Women

- A. HIV disease has a similar course in men and women. CD4 lymphocyte counts decline and opportunistic infections develop at the same rate in men and women, and women and heterosexual men with similar demographic characteristics seem to have similar survival rates.
- B. Pneumocystis carinii pneumonia is the most common AIDS-defining illness in women. Candida esophagitis, herpes simplex virus disease and cytomegalovirus infection are more common in women than in men. Kaposi's sarcoma is rare in women.
- C. Chronic vaginal candidiasis is often the initial clinical manifestation of HIV disease in women, developing much earlier than oral candidiasis.
- D. Invasive cancer of the cervix is an AIDS defining diagnosis. Other gender specific entities that affect disease classification include recurrent/persistent vulvovaginal candidiasis, cervical dysplasia (moderate, severe, or carcinoma in situ) and pelvic inflammatory disease, particularly if associated with tubo-ovarian abscess.

III. Initial Evaluation of the HIV-infected Women

- A. If pregnant, the patient should be informed that the risk of perinatal transmission is 15-35%, and she should be informed of the decreased rate of HIV transmission if AZT is used for herself and her neonate. If the HIV-infected patient is not pregnant, avoidance of pregnancy is advised.
- B. Safer sex practices or abstinence should be advised, including the use of condoms, decreasing the number of sex partners, and notification of partner(s) and referral.
- C. The patient should be educated about not sharing utensils which would lead to exchange of body fluids (e.g., toothbrushes, razors, drug apparatus) and about sanitary disposal of feminine napkins, tampons,

and hypodermic needles.

- D. Bleach should be used as an antiseptic for blood or secretion spills, or for needles.

IV. Gynecologic Complications and STDs

- A. Gynecologic infections in HIV-infected women are more likely to be severe, recurrent, and refractory as the CD4 cell count declines below 200/ μ L.

B. Genital Tract Neoplasia

1. In HIV-infected women, the incidence of HPV and squamous cell abnormalities are increased.
2. HIV-infected women are at high risk for cervical dysplasia. The lower a woman's CD4 cell count and the more advanced her HIV disease, the greater the incidence and severity of cervical dysplasia.
3. HIV positive women with cervical cancer tend to have more advanced disease at diagnosis, are more difficult to treat, and have a greater risk of recurrence.

C. Candidiasis

1. Recurrent yeast infections may be one of the earliest signs of HIV infection.
2. Candidiasis usually responds well to topical treatment early in HIV infection, but systemic therapy is often required for women with advanced HIV disease.

D. Pelvic Inflammatory Disease

1. There is an association of PID with HIV, and HIV positive women with PID are more likely to require hospital admissions, have adnexal masses, develop endometritis, and require surgical intervention.
2. Microbiologic etiology is unrelated to HIV status, and standard antibiotic treatment for PID works effectively in HIV-infected women.

- E. **Menses:** As the HIV disease progresses and women lose body mass, many women report amenorrhea or other menstrual irregularities.

V. Pregnancy and HIV Infection

- A. There is no definitive evidence that progression of HIV infection is accelerated by pregnancy, nor is there evidence that serious infection is more common in pregnancy.

B. Effect of Infection on Pregnancy

1. Transmission of HIV is primarily perinatal and occurs transplacentally, during labor and delivery, and during breast-feeding. HIV vertical transmission rates of 15-35% have been reported.
2. Breast feeding by mothers with infection, increases the risk of vertical transmission by 14%.
3. Some reports suggest high complication rates in women with advanced HIV disease, including low birth weight, preterm labor and birth, chorioamnionitis, premature rupture of membranes, fetal demise, and third trimester bleeding. At least one study showed an increased rate of spontaneous abortion in HIV-positive mothers.

VI. Management of the HIV-positive Pregnant Women

A. Counseling as to the risks to the fetus and options for abortion are provided.

B. Initial Prenatal Evaluation

1. Review of Systems: Symptoms that sometimes occur during pregnancy (nausea, fatigue, weight loss, anorexia, skin lesions, abdominal pain) may be difficult to differentiate from symptoms characteristic of HIV disease progression.

2. Routine Prenatal Labs

a. CBC, RPR or VDRL for syphilis, Hepatitis B surface antigen and antibody, urinalysis, rubella titer, blood type and antibody screen, pap smear, gonorrhea culture, and chlamydia test; toxoplasmosis titers and CMV titers; alpha-fetoprotein at 15-17 weeks.

b. CD4 counts and HIV viral load tests are recommended in every trimester.

3. Tuberculin testing is completed, and if the PPD is positive, a chest X-ray is done. If the X-ray is negative and the patient has no symptoms of active TB, then TB prophylaxis is indicated with isoniazid and B6.

4. Immunizations should be administered if indicated. MMR should be withheld until postpartum.

C. Follow-up Laboratory Monitoring: Repeating the CBC, CD4 cell count, viral load, RPR, Hepatitis B surface antigen (or antibody, if Hepatitis B vaccine was given), gonorrhea culture, and chlamydia test every trimester is recommended.

VII. Antiretroviral Therapy in Pregnancy

A. Maternal AZT therapy during pregnancy has been shown to reduce the HIV transmission rate by two thirds--from 25% to 8% without any adverse consequences for mother or child.

B. AZT therapy is recommended for all HIV-infected pregnant women during pregnancy regardless of CD4 cell count, even if they are already receiving didanosine (ddI), zalcitabine (ddC), or other agents.

C. Treatment for the newborn is recommended, regardless of whether the mother is treated.

D. For pregnant women, the AZT regimen consists of an antepartum dosage of 100 mg po five times daily, beginning between 14 and 34 weeks of gestation. The intrapartum dosage is 2 mg/kg IV over 1 hour, then 1 mg/kg/h until delivery. Newborns receive 2 mg/kg of AZT syrup PO q6h within 12 hours after birth, continuing for 6 weeks.

E. Zidovudine use in pregnancy has not been associated with teratogenicity; however, there is an increased risk of maternal and neonatal anemia. Prematurity, premature birth or congenital anomalies are not increased.

F. Once zidovudine has been initiated, CBC and liver function tests should be monitored.

G. Zalcitabine (ddC) in vitro data suggest that it has potential teratogenic effects and should be discontinued during pregnancy.

VIII. Opportunistic Infection Prophylaxis in Pregnancy

A. Treatment of HIV disease is not altered by the presence of pregnancy.

B. PCP Prophylaxis

1. TMP/SMX is recommended throughout pregnancy for those with

<200 CD4 cells, at dosages recommended for nonpregnant adults. Concerns about neonatal hyperbilirubinemia and kernicterus have not been proven to be a basis for withholding TMP/SMX.

2. Dapsone and pentamidine inhalation may also be used.
3. **MAC prophylaxis:** Rifabutin has not been studied during pregnancy and should be avoided.

IX. Management of Labor and Delivery

- A. Fetal exposure to maternal blood and vaginal secretions should be minimized. Internal scalp monitoring, scalp blood pH sampling operative rupture of membranes and episiotomy should be avoided. Only bulb or wall suction should be used to suction the infant's nares and mouth.
- B. Evidence suggests that cesarean section may reduce perinatal HIV transmission; however, additional trials are needed before definitive recommendations can be made.

X. Diagnosis of HIV-infection in Newborns of HIV-infected Women

- A. Nearly 90% of AIDS cases reported among children, and virtually all new HIV infections among children, are attributable to perinatal transmission of HIV.
- B. HIV antibody tests of the newborn reflect maternal HIV status because IgG antibodies cross the placenta.
- C. The sensitivity of viral culture and PCR is only about 40% at birth. The sensitivity of PCR and viral culture increases after one month, when the sensitivity of viral culture is about 90% and the sensitivity of PCR is perhaps higher.
- D. A positive diagnosis of HIV infection is confirmed by a positive PCR or HIV culture at birth, and a repeated positive PCR or HIV culture within one month. If the repeat test is negative, testing is repeated within one month until 2 concordant results are documented.
- E. A negative diagnosis is confirmed by a negative test at birth with PCR or HIV culture. The test is repeated at 1-3 months, and, if the test is still negative, repeat the test at 6 months. If tests remain negative, HIV antibody should be followed until seronegativity is documented.

References: See page 108.

Opportunistic Infections

Cytomegalovirus Retinitis

Cytomegalovirus (CMV) infection is extremely common in patients with AIDS and can result in esophagitis, colitis, and encephalitis. Ninety percent of AIDS patients develop active CMV infection as indicated by a positive culture.

I. Pathophysiology

- A.** Ocular disease caused by CMV is especially common in patients with AIDS. Clinical evidence of CMV retinitis occurs in 25% of AIDS patients, and CMV retinitis is present in up to 30% of patients at autopsy.
- B.** The threshold for risk of CMV retinitis begins at a CD4 count of about 100.

II. Diagnosis of CMV Retinitis

- A.** A complaint of persistent visual disturbances should lead to the diagnosis through a dilated eye exam by an ophthalmologist.
- B.** Virtually all patients with CMV retinitis have CD4+ lymphocyte counts of less than $50/\mu\text{L}$, and routine screening of patients with dilated, fundoscopic examinations should be initiated when cell counts decline to this level.
- C.** Symptoms of CMV retinitis may present as visual changes, including field defects, blurred vision, difficulty reading, or the perception of spots, flashes, or "floaters." The disease begins unilaterally but progresses to involve both retina. Systemic CMV infection also is frequently present, and gastrointestinal and neurologic disease may be present simultaneously.

III. Ophthalmologic Examination

- A.** Examination typically reveals large creamy to yellowish-white granular areas with perivascular exudates and hemorrhages ("cottage cheese and catsup" appearance), a finding that is virtually pathognomonic for cytomegalovirus. These abnormalities may be found initially at the periphery of the fundus, but if left untreated, the lesions progress.
- B.** The differential diagnosis of CMV retinitis includes candida infection, toxoplasmosis, syphilis, histoplasmosis, retinal scars, and cotton-wool spots. The disease progresses over weeks to a few months and, if untreated, inexorably leads to blindness.
- C.** Differentiating suspected CMV retinitis lesions from cotton wool spots is essential. Cotton wool spots appear as small, fluffy, white lesions with indistinct margins and are not associated with exudates or hemorrhages. They are common in AIDS patients and are usually asymptomatic. These lesions do not progress and often undergo spontaneous regression.
- D.** Toxoplasmosis is the second most common opportunistic infection of the eye but is characterized by little if any hemorrhage. It is associated with cerebral toxoplasmosis in the majority of patients.
- E.** Syphilis, herpes simplex, varicella-zoster virus (VZV), and tuberculosis are other infections that may rarely involve the retina.

IV. Treatment of Cytomegalovirus Retinitis

- A. Patients with suspected or confirmed CMV retinitis should be treated with ganciclovir or foscarnet. These agents are effective in the initial treatment of CMV chorioretinitis, although disease usually progresses despite continued treatment.
- B. Administration of intravenous ganciclovir is indicated for the initial treatment of acute CMV infection.

C. Ganciclovir (Cytovene)

1. Ganciclovir is a nucleoside analogue that differs from acyclovir by a single carboxyl side chain. This structural change confers 50 times more activity against CMV than acyclovir of inhibiting viral DNA polymerase.
2. Dosage is 5 mg/kg IV bid for 14-21 days, followed by maintenance of 5 mg/kg qd for 5 days a week. The dosage must be reduced with impaired renal function.
3. An intraocular ganciclovir implant may be used for CMV retinitis, providing sustained drug release for 5-8 months. The implant offers an alternative to multiple injections; however, this treatment does not affect extraocular CMV disease.
4. Initial response in retinitis (improvement or stabilization in vision of ophthalmoscopic appearance) occurs in approximately 75% of treated patients.
5. Maintenance therapy throughout the life of the patient is critical because the virus is only suppressed by ganciclovir and is not eliminated.
 - a. Oral ganciclovir is inferior to intravenous but may be considered for maintenance therapy (not induction) in patients who do not have immediate sight-threatening disease (i.e. retinitis near the macula or the optic nerve).
6. **Toxicity** frequently limits therapy with ganciclovir.
 - a. Leukopenia is usually reversible with dosage reduction, especially with the use of cytokines such as granulocyte colony-stimulating factor (G-CSF). Thrombocytopenia (platelet count less than 20,000/ μ L) occurs in 9%.
 - b. Central nervous system (CNS) side effects occur in 17% of AIDS patients. Confusion is the most common, occurring in 3%, and 2% experience convulsions, dizziness, headaches, or abnormal thinking.
 - c. Gastrointestinal disturbances occur in 15% of patients. Nausea is the most frequent complaint (5%), followed by vomiting (4%), abnormal liver function test (3%), and diarrhea (2%).
7. Ganciclovir plus zidovudine (AZT). The combination of zidovudine and ganciclovir is more toxic than either agent alone. Antiretroviral agents with less hematologic toxicity, such as didanosine (ddI), zalcitabine (ddC), or stavudine (D4T), are used when ganciclovir is being taken.

D. Foscarnet

1. Foscarnet inhibits the DNA polymerase of herpes viruses. The drug blocks the pyrophosphate-binding site of the viral DNA polymerase.
2. Foscarnet is used to treat patients with ganciclovir-resistant CMV.
3. Induction therapy is 60 mg/kg administered IV every 8 hours. Maintenance dosage has been 90 mg/kg in one daily infusion, but

120 mg/kg may provide superior benefit. Daily infusion of a 1 liter saline may reduce nephrotoxicity.

4. Adverse effects include renal impairment, anemia, hypocalcemia, hypomagnesemia, and hypophosphatemia. Dosage is adjusted in renal insufficiency.

E. Combination Therapy with Ganciclovir and Foscarnet for Relapsing Retinitis: Combination therapy with ganciclovir, 5 mg/kg/day, used together with foscarnet, 90 mg/kg/day, controls CMV retinitis more effectively than high dose ganciclovir 10 mg/kg or foscarnet 20 mg/kg alone.

F. Cidofovir

1. Cidofovir is a nucleotide analog that may prove to be useful in the treatment of CMV retinitis.
2. The major toxicity of cidofovir is nephrotoxicity. Concomitant administration of probenecid has protected against nephrotoxicity in animal models.

V. Prevention of CMV Disease: Prophylaxis is not recommended for CMV disease.

References: See page 108.

Fungal Infections in HIV-Infected Patients

I. **Candida Esophagitis**

- A. Candida esophagitis generally occurs in those with CD4 counts below 200 cells/ μ L.
- B. Symptoms most frequently include esophageal pain or odynophagia, nausea, mid-epigastric abdominal pain, and fever. Oropharyngeal mucosal candidiasis is often, but not uniformly, present.
- C. Empiric treatment for Candida esophagitis is indicated for patients with dysphagia or odynophagia who also have oral thrush. Endoscopy with biopsy and cultures is indicated if there is failure to respond within 1 week.
- D. The diagnosis is characterized endoscopically by adherent, whitish mucosal plaques and superficial mucosal ulcerations of the esophagus; the disorder is confirmed by demonstration of Candida in tissue biopsy or culture.
- E. **Treatment of Candida Esophagitis**
 1. Fluconazole (Diflucan) 200 mg PO or IV qd for 14-21 days or
 2. Amphotericin B 20 mg IV QD for 10-21 days or
 3. Ketoconazole 200 mg PO BID or
 4. Itraconazole (Sporanox) 200 mg/d PO BID for 10-21 days.
- F. **Chronic suppressive therapy** with fluconazole, ketoconazole or itraconazole may be required for those with repeated episodes of esophagitis.
- G. Primary prophylaxis is not currently recommended because resistant Candida may emerge.

II. **Mucosal Candidiasis**

- A. The prevalence of oral candidiasis in HIV infection is high, occurring in up to 15%, with a wide range of CD4 cells being affected. The incidence rises as the CD4 count falls.
- B. Thrush candidiasis (pseudomembranous candidiasis) is characterized by white or creamy plaques on the oral mucosa. These white plaques can be removed, often revealing a bleeding surface.
- C. Erythematous candidiasis appears as a flat red lesion, which may be found on the hard or soft palate, dorsal surface of the tongue, or on other mucosal locations. When candidiasis affects the dorsal surface of the tongue, patchy depapillated areas appear.
- D. The diagnosis of oral candidiasis may be made from smears, examined by potassium hydroxide suspension showing hyphae and blastospores.
- E. **Treatment of Mucosal Candidiasis**
 1. Among patients with early HIV disease (CD4 counts of greater than 300), topical therapy is usually sufficient for mucosal Candidiasis. As the CD4 count approaches 100 or less, systemic therapy is often necessary.
 - a. Clotrimazole (Mycelex) troches 10 mg dissolved slowly in mouth 5 times/d.
 - b. Fluconazole (Diflucan), 100-200 mg po qd; higher dosages may be necessary.
 - c. Ketoconazole (Nizoral), 400 mg po qd 1-2 weeks or until resolved.
 2. Resistant Candida species develop with increasing frequency in

patients with very advanced disease (CD4 count less than 25).

3. Treatment of resistant *Candida* involves switching to an alternative agent (e.g. from fluconazole to itraconazole). In difficult to treat cases, systemic amphotericin B is usually effective, although a few patients may demonstrate a minimal response.

III. Cryptococcosis

- A. Cryptococcosis has an incidence of 6-10% and occurs most commonly in those with advanced immunosuppression with CD4 lymphocyte counts of less than 50 cells/ μ L.
- B. Meningoencephalitis is the most common presentation of cryptococcus in patients with AIDS. Onset is often insidious, and symptoms include fever, headache, nausea, dizziness, somnolence, mental status changes, or seizures, obtundation and coma.
- C. Pulmonary disease and extrapulmonary disseminated disease occur less commonly. Sites of extrapulmonary disease include skin, bone, prostate gland, adrenal gland, kidney, pericardium, endocardium, liver, and the retina.
- D. **Culture of CSF** is the most reliable diagnostic test for detection of the organism.
- E. **Cryptococcal Antigen (CRAG):** A positive serum CRAG and/or CSF CRAG is highly sensitive and is present in >92% of patients with cryptococcal meningitis or disseminated cryptococcal disease.
- F. **The CSF profile** for those with meningitis generally shows a pattern consistent with aseptic meningitis in which the cell count is less than 100-500 with a lymphocytic predominance, the glucose is normal to mildly decreased, and the protein is normal to mildly increased. Fungal cultures will be positive.
- G. **Management of AIDS-associated Cryptococcal Disease**
 1. Amphotericin B at 0.7 mg/kg per day for 7 to 14 days or until clinically stable (maximum total dosage of 2 g), followed by fluconazole 400 mg qd to complete 10 weeks of therapy.
 - a. Fluconazole is less effective than amphotericin B for initial therapy. Fluconazole may be appropriate for mild, low titer disease if oral treatment can be tolerated; 400-800 mg po qd, for 8-12 weeks.
 2. Aggressive management of increased intracranial pressure is important. Serial lumbar punctures, lumbar drains, and, when necessary, ventricular peritoneal shunts have been associated with decreased morbidity and mortality.
 3. **Maintenance Suppressive Therapy:** Chances of sterility-cure are poor (50%); therefore, chronic suppressive therapy is indicated with fluconazole, 200 mg qd.
- H. **Primary Prophylaxis** is not recommended. Primary prophylaxis with fluconazole significantly reduces the incidence of cryptococcal meningitis but it does not appear to provide a survival benefit.

IV. Histoplasmosis

- A. Histoplasmosis is a fungus endemic in the Ohio and Mississippi river valleys and central and northern South America. The fungus grows in soil enriched with bird and bat droppings.
- B. Disease can occur in all stages of HIV infection, although it is more common in patients with CD4 counts of less than 500 cells/ μ L.

C. Clinical Presentation

1. Disseminated disease usually presents with "fever of unknown origin", night sweats, malaise, soft small nodular infiltrates, hepatosplenomegaly (20-40%), and progressive weight loss.
2. Often these symptoms are accompanied by abdominal pain, hepatosplenomegaly, lymphadenopathy, diarrhea, and headache. Respiratory symptoms, with non-productive cough and dyspnea, are also common.
3. **A sepsis syndrome** occurs in 10% at presentation, with fever, hypotension, renal and hepatic failure, adult respiratory distress syndrome, and coagulopathy (DIC).
4. Central nervous system manifestations occur in 5-20% of AIDS patients with histoplasmosis. Syndromes include meningitis, encephalopathy, and focal parenchymal granulomatous lesions.

D. Diagnosis

1. The diagnosis is based on culture of blood or any involved organ, or tissue biopsy.
2. Blood cultures with lysis-centrifugation are positive in 85-95% but require 2-3 weeks for results. Buffy coat of peripheral blood or bone marrow by Wright-Giemsa is positive in up to 50%.
3. Histoplasma antigen can be measured in serum, urine and other normally sterile body fluids and may provide ancillary evidence of infection and can be used to monitor therapy.

E. Treatment of Disseminated Histoplasmosis in AIDS

1. Amphotericin B is the treatment of choice; 0.7 to 1 mg/kg/d, for a total dose of 15 mg/kg, over a six to 10 week period. Amphotericin is 90% effective. Fever drops rapidly to less than 100° F in 7 days in 75%.
2. Itraconazole is 85% effective. Itraconazole, 400 mg PO qd x 12 weeks, is recommended in histoplasmosis cases that are non-meningeal and nonseptic shock; amphotericin is recommended in other patients.
3. Maintenance antifungal therapy is necessary to prevent relapse. Itraconazole, 200 mg qd, prevents relapse in 95%.

V. Aspergillosis

- A. Aspergillosis in patients with AIDS occurs as a sporadic infection seen most often in patients with advanced HIV disease with CD4 lymphocyte counts of <50 cells/ μ L.
- B. The presentation includes pulmonary pneumonitis with diffuse interstitial infiltrates, widespread multiorgan disease, and fungemia
- C. Nonspecific symptoms of fever, cough, chest pain, dyspnea, or hemoptysis may precede more specific symptoms referable to the portion of the respiratory tract involved.

D. Diagnosis

1. The diagnosis is based on recovery of *Aspergillus* spp. in culture of sputum or other specimens coupled with biopsy.
2. Bronchoscopic visualization of a tracheobronchial pseudomembrane coupled with culture or biopsy will confirm pseudomembranous tracheobronchitis.

E. Treatment of Aspergillosis

1. Systemic amphotericin B is the treatment of choice; a dose of 1-1.5

mg/kg/d should be administered and continued to a total of 2-3 grams over a 6-12 week course.

2. Itraconazole 200-400 mg BID has been used with some success in immunocompromised patients and can be used as salvage therapy for those who have failed amphotericin B.
3. Clinical response is often slow, relapse appears to be common, and overall morbidity and mortality are high despite treatment.

VI. Coccidiomycosis

- A. Coccidioidomycosis is a soil fungus endemic in the southwestern United States (California, Arizona, New Mexico, Texas), northern Mexico, and Central and South America.
- B. Clinical presentation is characterized by diffuse pulmonary disease with fever, dyspnea, and night sweats, but also focal lung involvement, discrete nodules, hilar adenopathy, cavitory disease and pleural effusions.
- C. Coccidioidomycosis is frequently associated with disseminated disease and CNS involvement is common.
- D. Rarely, Coccidiomycosis may cause extrapulmonary findings such as cutaneous and meningeal involvement (high CSF WBC and protein with low sugar with 50% negative cultures).

E. Diagnosis

1. Focal infiltrates may be seen in minimally immunosuppressed patients. Interstitial disease is seen in severely immunocompromised individuals.
2. The organism can be identified by culture or biopsy stains. Blood cultures are positive in <30%
3. Serologic tests are positive in >80%. Complement fixation and immunodiffusion test for IgG are useful for diagnosis of acute infection with few false positives.

F. Treatment of Coccidiomycosis

1. **Treatment of Life-threatening Disease:** Amphotericin is recommended as initial therapy at a dose of 1 mg/kg/d to a total dose of 700 mg or until clinically stable, then either fluconazole or itraconazole at 400 mg qd. Liposomal amphotericin B is equally effective as amphotericin B but has less renal toxicity.
2. For less sick patients, an imidazole alone is adequate therapy.

VII. Other Systemic Fungal Infections

- A. Other sporadic or geographically localized fungal infections reported in patients with AIDS include disseminated blastomycosis, sporotrichosis, aureobasidiosis, Fusarium infection, Trichosporon begelei infection, and Penicillium marneffei infection.
- B. Patients at risk are generally those with advanced immunosuppression.
- C. Blastomycosis has been described most frequently in the southeastern and central Midwestern U.S. Sporotrichosis results from exposure to contaminated soil and is seen most frequently in gardeners and floral workers. Penicillium marneffei infections are endemic in Thailand and southeast Asia and sporadic in other patient populations.
- D. Clinical manifestations are generally those of disseminated fungal infection, including fever, night sweats, weight loss, and evidence of multiorgan dysfunction.

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- E. The diagnosis requires a high index of clinical suspicion, an appropriate epidemiologic and exposure history, and fungal culture of specimens obtained from involved tissue or histopathologic biopsy.
- F. **Treatment of Choice** for most serious, invasive, or disseminated fungal infections is amphotericin B. Alternative options for blastomycosis include itraconazole and ketoconazole.

References: See page 108.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is the most common neoplasm affecting HIV-infected individuals. It is seen in approximately 17% of gay men with AIDS and 1-5% of other persons with HIV infection.

KS remains almost exclusively confined to the homosexual male population. Kaposi's sarcoma as a proportion of all AIDS-defining diagnoses is less frequent among IV drug users.

I. Pathophysiology

- A. The sexually transmitted human herpes virus #8 (HHV-8) is found in Kaposi's sarcoma tissue from patients with AIDS. This virus has been identified in greater than 90% of KS biopsies.
- B. Kaposi's sarcoma may be the presenting sign of HIV disease. Lesions that appear after the occurrence of opportunistic infection often have a more aggressive clinical course.

II. Clinical Presentation of Kaposi's Sarcoma

A. Kaposi's Sarcoma of the Skin

1. KS may present as palpable, firm, non-tender, cutaneous nodules, ranging from 0.5 to 2 cm in diameter. Early, small, non-palpable lesions often resemble small ecchymosis.
2. Lesions may also appear as small raised plaques, nodules or large bulky plaques. They are generally non-pruritic and painless; however, lesions at any site may become painful or locally uncomfortable.
3. The color of lesions range from brown to pink to deep purple, but they may appear brown or black in dark-skinned individuals. The lesions can be found on any body surface but have a predilection for the upper body and head and neck areas.
4. Dermal and lymphatic infiltration with tumor can cause edema of the extremity, genitals and periorbital areas and may be complicated by local skin breakdown and bacterial cellulitis. Lesions on the feet can cause pain and difficulty walking.
5. **Differential Diagnosis:** Bacillary angiomatosis, cutaneous mycobacterial disease, cutaneous fungal disease, and angiosarcoma.
6. Epidermal KS may be diagnosed based on the clinical appearance; however, biopsy is recommended.

B. **Oral lesions** are common and may be the first site of disease. They are often asymptomatic but can produce pain, difficulty swallowing, gingival bleeding and dental displacement.

C. **Visceral disease** occurs commonly.

1. The GI tract is the most common site, and it may be involved in up to 40% of patients at diagnosis.
2. Symptoms such as bleeding, perforation, and obstruction are uncommon.
3. Gastrointestinal KS has a typical red, raised appearance.

D. **Pulmonary KS** generally presents with dyspnea, cough or bronchospasm. Fever is usually absent.

1. Pulmonary KS typically has radiographic findings of diffuse, reticular-nodular infiltrates and sometimes pleural effusion. The definitive diagnosis requires transbronchial or open lung biopsy.

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2. Thallium or technetium-99m scanning may help differentiate pulmonary KS because Kaposi's sarcoma is thallium and technetium avid, whereas lymphoma and infection are gallium avid.
3. Pulmonary disease may progress rapidly to respiratory failure and may be difficult to distinguish from an infectious process.

E. Bone marrow or central nervous system involvement with KS is exceedingly rare.

III. Treatment of Kaposi's Sarcoma

A. Local therapy is appropriate for symptomatic local involvement and small lesions that are cosmetically unsightly.

1. **Cryotherapy:** Liquid nitrogen is usually successful for small cosmetically unsightly skin lesions, but it may leave a hypopigmented area.
2. **Intralesional Vinblastine:** 0.01 mg vinblastine in 0.1 mL sterile water may be injected into each lesion. Repeated treatments may be necessary; a hyperpigmented area frequently remains.
3. **Radiotherapy** is highly effective for facial edema. It is less effective than chemotherapy for lower extremity edema.

B. Systemic chemotherapy is indicated for widespread symptomatic disease, rapidly local progressive disease, and for visceral disease.

1. **Liposomal Anthracyclines:** Liposomal preparations of both doxorubicin and daunorubicin are highly efficacious as single agents. Response rates are 30-74%. Alopecia and neuropathy is less severe than with the ABV regimen, and the response rate to liposomal doxorubicin is significantly higher.
2. **Combination Regimens**
 - a. Patients with poor bone-marrow reserve should be treated with bleomycin and vincristine, since neither are myelosuppressive.
 - b. The doxorubicin, bleomycin, vincristine (ABV) regimen is most commonly employed for patients with advanced symptomatic disease who require a rapid response to therapy.

Chemotherapy Regimens

Agents	Dose	Response Rate	Recommended Use
Liposomal Daunorubicin	40 mg/m ² q2 weeks	28-55%	Single agent of first line therapy
Liposomal Doxorubicin	20 mg/m ² q2-3 weeks	45-74%	Single agent for refractory disease
Vincristine/ Vinblastine	2 mg 0.1 mg/kg	45%	Diffuse, disease, minimally symptomatic. Use each drug on alternate weeks
Adriamycin/ Bleomycin/ Vincristine	10-20 mg/m ² 10 mg/m ² q 14d 2 mg	87%	Diffuse symptomatic disease, edema, rapid response desired

Bleomycin/ Vincristine	10 mg/m ² q 14d 2 mg	45%	Diffuse disease, symptomatic, patients with neutropenia or poor bone marrow reserve
Taxol	100 mg/m ² q2 weeks	53%	Indicated for treatment failures

C. Alpha-Interferon

1. Interferon is an effective regimen recommended for diffuse progressive disease, but with minimal symptoms and a CD4 lymphocyte count $>100/\mu\text{L}$; the response rate is 30-40%.
2. Some level of intact immune function is required in order for the drug to achieve response. Those with <200 CD4 cells have a response rate of $<10\%$.
3. Low doses of interferon-alpha (<10 million units/day, 5 days/week) in combination with a nucleoside analog (e.g., zidovudine, didanosine, or zalcitabine) have shown higher response rates than with interferon alone.
4. Many patients relapse within 6-8 months after discontinuation of interferon, and continued treatment may be necessary.

D. Radiation Therapy

1. Radiation therapy is much less effective than chemotherapy and is primarily used for palliation of symptomatic disease or for cosmetic improvement of disfiguring lesions.
2. Radiation therapy may be helpful in alleviating pain and bleeding, and in lessening localized facial and extremity edema, and in shrinking obstructing lesions.

IV. Therapeutic Recommendations

A. Local Cosmesis

1. Cryotherapy
2. Intralesional chemotherapy
3. Radiotherapy

B. Locally Symptomatic

1. Radiotherapy
2. Laser therapy for oral lesions

C. Minimal But Rapidly Progressive Disease

1. Vincristine and vinblastine
2. Alpha interferon with zidovudine if $\text{CD4} \geq 100$ cells/ μL

D. Widespread Symptomatic Disease

1. Liposomal Anthracyclines
2. Adriamycin, bleomycin, vincristine (ABV)

E. Cytopenic Patients

1. Vincristine and/or
2. Bleomycin
3. Myeloid CSF is added

References: See page 108.

AIDS-Related Malignancies

A malignancy will develop in approximately 40% of all patients with AIDS sometime during the course of their illness. Lymphoma should be considered whenever an HIV/AIDS patient presents with fever of unknown origin.

Cervical preinvasive lesions such as cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia can often be detected by Pap smear and biopsy. Kaposi's sarcoma is the most common malignancy in HIV/AIDS patients, and it may occur relatively early in the course of disease. (See "Kaposi's Sarcoma," page 89.)

I. HIV-Associated Non-Hodgkin's Lymphoma

A. Epidemiology

1. B-cell lymphoma is a non-Hodgkin's Lymphoma (NHL) that occurs in 5-10% of individuals with HIV infection.
2. Lymphomas account for 12-16% of all AIDS-related deaths.

B. AIDS-related lymphoma is seen more frequently in men than in women, and is twice as common in whites as in blacks. The incidence of lymphoma is 60 times higher in the HIV population than in the general population.

C. Patients with AIDS-related lymphoma tend to present with advanced HIV disease. The median CD4 count for patients with systemic lymphoma is 100-200 cells/ μ L, and CD4 counts are usually <50 cells/ μ L in the majority of patients with CNS lymphoma.

D. Clinical Evaluation

1. Extra-nodal involvement is common, and sites include the central nervous system in 30%, gastrointestinal tract in 25%, and bone marrow in 25%. Any other site in the body can also be involved including the rectum, soft tissue, oral cavity, lung, heart and other organs.
2. Fever, night sweats, and weight loss of more than 10%, accompanied by enlarged and asymmetrical lymph nodes, or a discrete mass in an organ or in soft tissue, should raise a suspicion of non-Hodgkin's lymphoma.
3. Diagnosis of non-Hodgkin's lymphoma requires histologic confirmation by biopsy of a lymph node or other organ.
4. A complete staging evaluation should include CT or MRI scans of the head, chest and abdomen, bone marrow aspiration and biopsy, liver function studies, and spinal fluid analysis.

E. Prognosis

1. Factors That Correlate with Poor Survival

- a. A history of opportunistic infection prior to lymphoma
 - b. CD4 counts <200 cells/ μ L
 - c. Karnofsky performance status <70%.
 - d. Stage-4 disease, especially if due to bone marrow involvement.
2. Median survival in patients who lack these findings is typically 11-12 months, while median survival is approximately four months for patients with one or more adverse prognostic features.

F. Management of HIV-associated Lymphoma

1. Chemotherapy has demonstrated a greater than 50% complete response rate, with a long-term lymphoma-free survival of 60% in patients with complete responses.

2. Treatment is frequently complicated by opportunistic infections and by poor bone marrow reserve.
3. Relapse occurs in 25-50% within 6 months. Median survival is 4-7 months with about half dying of lymphoma and half of opportunistic infection.

II. Primary Central Nervous System Lymphoma

- A. Primary CNS lymphoma often presents with focal neurologic deficits, seizures, and/or altered mental status. Any site in the brain may be involved, and one to four space occupying lesions are usually seen on MRI or CT scan.
- B. These individuals present with severe immunodeficiency, most with CD4 lymphocyte counts <50 cells/ μ L.
- C. Toxoplasma therapy is appropriate in those individuals who are toxoplasma seropositive. Patients who are seronegative should receive a brain biopsy to rule out the presence of lymphoma.
- D. The standard approach to treatment is whole brain radiotherapy. Three quarters of patients will have a clinical response to therapy; however, survival is improved only from a median of 1.4 months to 4.5 months.

III. Cervical Carcinoma

- A. Cervical carcinoma in the setting of HIV infection is an AIDS-defining malignancy.
- B. Cervical intraepithelial neoplasia is also seen in association with HIV infection and is a premalignant lesion for squamous cell carcinoma.
- C. HIV positive women have up to a tenfold increased risk of abnormal cervical cytology. Abnormal cytology occurs at rates of 30-60%, and PAP smears consistent with cervical dysplasia develop in 15-40%. The prevalence of cervical dysplasia increases with progressive immunodeficiency.
- D. CD4 lymphocyte counts of <200 cells/ μ L are associated with higher grade CIN than are higher levels of immune function.

E. Diagnosis and Screening

1. Post-coital bleeding with serosanguinous and/or foul-smelling vaginal discharge are usually the first symptoms of more advanced invasive disease.
2. Lumbar-sacral pain or urinary obstructive symptoms may indicate advanced disease.
3. HIV-infected women should have pelvic examinations and Pap smears every 6 months with careful inspection of vulvar, vaginal, and anal epithelium.
4. PAP smears indicating CIN or other abnormalities, justify colposcopic evaluation.
5. For women who have a history of CIN, more frequent reevaluation and cytologic screening is undertaken, as well as post-therapy colposcopy.
6. The majority of cervical carcinoma is of the squamous cell type. Women with cervical carcinoma typically present with more advanced disease and have a more aggressive clinical course.

F. Medical Treatment

1. Treatment of pre-invasive disease includes cryotherapy, laser therapy, cone biopsy, and excision. Short-term recurrence rates of

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40-60% have been reported.

2. For patients with cervical carcinoma, the same principles that guide oncologic management in the immunocompetent patient are utilized, including surgery and radiation therapy.

IV. Anal Carcinoma

- A. Although anal carcinoma is not currently an AIDS-defining illness, the incidence of this tumor in the HIV-infected population is increasing. Among homosexual men the incidence of anal carcinoma is between 25-87 per 100,000 compared with 0.7 per 100,000 in the entire male population.
- B. The majority of patients with anal carcinoma have squamous cell carcinoma.
- C. Patients with severe immunosuppression (i.e., CD4 <50 cells/ μ L) present at a more advanced stage and have more aggressive disease.
- D. **Etiology and Risk Factors**
 1. An association between the presence of HPV and anal intraepithelial neoplastic lesions has been demonstrated. Abnormal cytology predicts the later development of invasive carcinoma.
 2. Individuals with a history of perianal herpes simplex, anal condyloma or multiple sexual partners with anal receptive behavior are at greater risk for developing this tumor.
 3. High grade AIN and HPV isolation becomes more common as immune function declines.
- E. **Signs and Symptoms:** Rectal pain, bleeding, discharge and symptoms of obstruction or a mass lesion are the most frequent presenting symptoms.
- F. **Medical Management**
 1. Patients with local intraepithelial neoplasia are treated with cryotherapy or topical 5-fluorouracil. The recurrence rate is high.
 2. For patients with squamous cell carcinoma of the anus, chemotherapy followed by radiation therapy can produce high rates of complete remissions.
- G. **Screening for Anal Neoplasia in HIV-infected Patients with a History of Anal Intercourse**
 1. Anal Pap smear
 2. Anoscopy on a routine basis
 3. Biopsy of any abnormality identified on anoscopy
 4. Frequent anoscopic follow-up if abnormalities were identified previously

References: See page 108.

Mycobacterium Avium Complex Disease

Mycobacterium avium complex (MAC) infection is among the most common opportunistic infections occurring in persons with AIDS. The organisms are ubiquitous in the environment--found in soil, water, and in a variety of animals and foods. The incidence of disseminated MAC disease is 40% in patients with AIDS.

The risk of developing disseminated MAC disease is greatest for those who have CD4 lymphocyte counts below 50-75 cells/ μ L and who have had a prior opportunistic infection.

I. Clinical Manifestations of Mycobacterium Avium Complex Disease

- A. Most patients with AIDS and MAC disease have disseminated multiorgan involvement. The most frequent symptoms are fever, night sweats, weight loss, wasting, weight loss, fatigue, diarrhea, and abdominal pain.
- B. Physical findings commonly include hepatomegaly, splenomegaly, and intra-abdominal lymphadenopathy (demonstrated by x-ray). Peripheral lymphadenopathy is uncommon.
- C. Other symptoms and laboratory abnormalities reflect local sites of involvement such as pneumonitis, pericarditis, osteomyelitis, skin lesions, soft tissue abscesses, or central nervous system lesions; localized disease syndromes such as these are uncommon in this patient population (i.e, disseminated disease is more common).
- D. The most frequently identified laboratory abnormalities are anemia (usually severe [hematocrit <30] or out of proportion to that expected with other underlying conditions or medications such as ZDV) and elevated alkaline phosphatase.

II. Diagnosis of Mycobacterium Avium Complex Disease

- A. The diagnosis of disseminated MAC disease is based on recovery of MAC from blood (with lysis centrifugation) or bone marrow cultures. Recovery of MAC from other body fluids or tissue, such as cerebrospinal fluid or biopsy samples, accompanied by systemic symptoms, provides presumptive evidence of disseminated disease.
- B. A positive acid-fast bacillus (AFB) smear is non-specific and until culture and species identification is available, the finding of AFB in specimens indicates Mycobacterium tuberculosis infection.

III. Treatment of Mycobacterium Avium Complex

- A. Patients with AIDS and MAC disease should be treated with an initial regimen consisting of a combination of at least two anti-mycobacterial agents to delay the emergence of resistance.
- B. Oral clarithromycin (Biaxin), 500 mg BID or azithromycin (Zithromax) 500-1000 mg/d are the preferred first agents.
- C. Ethambutol (15 mg/kg/d) is the most common choice as a second agent.
- D. Rifabutin (Mycobutin), 300 mg/d, may be added when the clinical situation warrants more intensive therapy.
- E. Most patients require 2-8 weeks of treatment before a substantial reduction in clinical symptoms can be demonstrated. Maintenance therapy should be continued for life.

IV. Prophylaxis Against Mycobacterium Avium Complex Disease

- A. Prophylaxis should be considered for persons with AIDS and a CD4 lymphocyte count of <100 cells/ μ L; some experts wait until the CD4 count is <50 cells/ μ L.
- B. Clarithromycin (Biaxin) 500 mg BID may reduce the incidence of disseminated MAC from 15 % to 5% and is associated with improved survival.
- C. Azithromycin (Zithromax), 500 mg three times per week reduces the incidence of MAC bacteremia by 50%.
- D. Rifabutin (Mycobutin), 150 mg PO bid, reduces the incidence of MAC bacteremia by 50%, it may be associated with improved survival.
 - 1. Rifabutin lowers zidovudine and clarithromycin levels, and fluconazole increases rifabutin levels. Rifabutin may increase metabolism of other drugs.
 - 2. Uveitis is seen with elevated levels that may be prompted by the coadministration of fluconazole. Discoloration of body secretions, neutropenia, and hepatitis occur.

References: See page 108.

Pneumocystis Carinii Pneumonia

The greatest risk for PCP occurs at a CD4 count of less than 200 cells/ μ L. There is a gradient of risk as the CD4 cell count decreases, with a small proportion of cases occurring at a CD4 higher than 200, and a greater risk of PCP at a CD4 below 100. In children, a CD4 <20% is the strongest predictor of risk.

I. Diagnosis

A. Symptoms of PCP include progressive dyspnea, nonproductive cough, fever, night sweats and fatigue. A productive cough may sometimes be noted in PCP.

B. Diagnostic Procedures

- 1. Chest x-ray** usually reveals diffuse, interstitial infiltrates; however, x-ray findings can often be normal or atypical.
- 2. Induced Sputum Stain:** If performed properly, induced sputum examination can diagnose 85-95% of cases of PCP. Yield is improved with fluorescent monoclonal antibody stains. A negative sputum stain should be followed by a bronchoalveolar lavage to definitively rule out infection.
- 3. Bronchoalveolar lavage (BAL)** should be performed in patients in whom the level of suspicion for PCP is high and in whom induced sputum examination is negative.
- 4. Diffusion Capacity for Carbon Monoxide (DL_{co})** may be useful for patients with a clinical suspicion for PCP who have a normal or atypical chest x-ray.
- 5. High Resolution CT Scan:** Absence of typical changes (i.e. ground glass opacities) on this test may be useful to exclude PCP, but results may be falsely positive.

II. Treatment of Pneumocystis Carinii Pneumonia

A. Treatment for Mild to Moderate PCP Disease

1. Oral or IV trimethoprim-sulfamethoxazole DS 160/800 mg (Bactrim, Septra); 15-20 mg/kg of the trimethoprim component daily in three divided doses (two double strength tabs tid) for 21 days. Alternative drugs may be used if treatment-limiting adverse effects occur or if there is failure to respond to TMP-SMX.
2. Clindamycin 600 mg po tid plus primaquine 30 mg/d
3. Aerosolized pentamidine 300 mg/d
4. Adjunctive corticosteroids are recommended for patients with a room air A-a gradient ≥ 35 or a room air $pO_2 < 70$ mm Hg; prednisone 40 mg po twice daily x 5 days, then 40 mg once daily for five days, then 20 mg once daily for the remainder of PCP therapy.

B. Treatment of Severe PCP Disease

1. IV TMP-SMX 15 mg of trimethoprim component/kg/d in 3 divided doses (20 mL of IV solution in 100 mL of D5W IVPB q8h) [solution for injection: 80/400 mg/5 mL].
2. If the patient is unable to take TMP-SMX, pentamidine (Pentam 300) IV may be used; 4 mg/kg IV infusion daily for 21 days. Nephrotoxicity and hypoglycemia are significant adverse effects.
3. Clindamycin 600 mg IV q8h plus oral primaquine 300 mg/d is an alternative.

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- C. Steroids are used when the pO2 is <70 or the A-a gradient is greater than 35. Steroids should be started early (within 72 hours of the diagnosis); prednisone 40 mg PO bid x 5 days, then 40 mg qd x 5 days, then 20 mg qd to end of treatment.

III. **Pneumocystis Carinii Pneumonia Prophylaxis**

A. **CDC Criteria for Initiating Prophylactic Therapy**

1. CD4 cell count less than 200 cells/ μ L
2. The percentage of CD4 cells is less than 20% of lymphocytes
3. A previous episode of PCP has occurred
4. Constitutional symptoms are present, such as thrush or unexplained fever >37.8°C for two or more weeks.

B. Prophylaxis is taken indefinitely, and is continued even if the CD4 count rises above 200 cells/ μ L (as the result of antiretroviral therapy).

C. **Trimethoprim/sulfamethoxazole (Bactrim, Septra)** is the drug of choice; one double-strength tablet PO daily 3 times per week or one single-strength tab daily. TMP/SMZ is dually preventative against toxoplasmosis.

1. Patients taking TMP/SMZ therapy are monitored for leukopenia, anemia, thrombocytopenia, fever, rash (including Stevens-Johnson syndrome), azotemia, nausea, hepatitis, pruritus, and elevated transaminase levels.
2. Desensitization is often used if the drug reaction was mild.

Trimethoprim/Sulfamethoxazole Desensitization

1. Dilute 1 cc of TMP/SMX pediatric suspension in 20 cc of water.
2. Use the diluted solution on days 1-4. Use undiluted pediatric suspension on days 5-9. Use double strength TMP/SMX tablets on days 10-18.

<u>Day</u>	<u>Medication</u>	<u>Amount</u>
1	Diluted suspension	1.0 cc
2	Diluted suspension	2.0 cc
3	Diluted suspension	4.0 cc
4	Diluted suspension	8.0 cc
5	Undiluted suspension	0.6 cc
6	Undiluted suspension	1.25 cc
7	Undiluted suspension	2.5 cc
8	Undiluted suspension	5.0 cc
9	Undiluted suspension	10 cc
10	TMP/SMX DS tablet	½ tab once daily
11	TMP/SMX DS tablets	½ tab twice daily
12	TMP/SMX DS tablets	½ tab twice daily
13	TMP/SMX DS tablets	½ tab twice daily
14	TMP/SMX DS tablets	½ tab twice daily
15	TMP/SMX DS tablets	½ tab twice daily
16	TMP/SMX DS tablets	½ tab twice daily
17	TMP/SMX DS tablets	½ tab twice daily
18	TMP/SMX DS tablets	1 whole tablet once daily

3. Notify physician immediately if itching, rash, shortness of breath, nausea, vomiting, diarrhea, fever, or any other unusual symptoms occur.

D. **Dapsone** is an alternative agent; 50 mg PO bid, 100 mg twice a week or 200 mg once a week; contraindicated in G6PD deficiency.

E. **Pentamidine (NebuPent)** is another alternative agent; 300-mg (one

vial in 6 mL sterile water) once a month via jet nebulizer (Respirgard II).

F. Alternative Prophylaxis Therapies

1. Pentamidine, 4 mg/kg once-monthly intramuscular or intravenous therapy: The data is scant, but this treatment may have possibly adequate efficacy. Monitor for pancreatitis in patients receiving concomitant ddl
2. Dapsone-pyrimethamine: 200 mg/wk plus 25-75 mg/wk OR 50 mg/wk plus 50 mg/wk. This regimen is less effective than TMP-SMX; however, it may offer protection against toxoplasmosis in toxoplasma antibody-positive individuals.

References: See page 108.

Toxoplasmosis

The diagnosis of toxoplasmic encephalitis in AIDS patients is by clinical inference based on the results of serology for *Toxoplasma gondii*, findings on CT/MRI scans, and response to toxoplasmosis therapy.

I. Clinical Evaluation

- A. Toxoplasmosis occurs in 5-10% of patients with AIDS, presenting with fever, altered mentation, seizures, and focal neurologic signs that develop subacutely over a few days. It is the most common cause of isolated CNS disease in HIV-infected patients.
- B. Patients who are more likely to have toxoplasmic encephalitis are those who have a positive *T. gondii* serology (IgG antibody) and who have at least two focal cerebral lesions on MRI or CT (a single lesion has a high probability of being due to lymphoma rather than to *T. gondii*).
- C. A negative toxoplasmosis antibody titer makes the diagnosis of toxoplasmosis encephalitis unlikely. The false negative rate of the antibody titer is only 1-2%. A brain biopsy should be considered in these patients.
- D. Patients who have responded both clinically and radiologically to 7 days of treatment for toxoplasmosis are also more likely to have toxoplasmosis.
- E. Toxoplasmosis may also cause pulmonary infection and disseminated disease (presenting as severe sepsis and a positive bone marrow biopsy).

II. Acute/Primary Treatment of Toxoplasmosis

Drug	Dosage Schedule
Pyrimethamine Folinic acid (Leucovorin)	Oral 200 mg loading dose, then 50-75 mg qd Oral, IV, or IM 10 to 20 mg qd (up to 50 mg qd)
plus Sulfadiazine or (if allergic to sulfadiazine) clindamycin	1 to 1.5 g PO q6h 600 mg PO or IV q6h (up to 1200 mg q6h)
Possible Alternative Regimens a. Trimethoprim/sulfameth- oxazole	5 mg of trimethoprim component/kg PO or IV q6h
b. Pyrimethamine and folinic acid i. Clarithromycin ii. Azithromycin iii. Atovaquone iv. Dapsone	Dosage as in standard regimens plus one of the following 1 g PO q12h 1200-1500 mg PO qd 750 mg PO q6h 100 mg PO qd

- A. Acute therapy is recommended for a minimum of 3 weeks depending on clinical and radiologic response. Acute therapy should be continued for 4-6 weeks in patients who are more seriously ill and who have not had a complete clinical response or imaging response (CT or MRI).

- B.** Clinical response should occur in 7 days, but radiologic response may lag considerably behind clinical response. If clinical improvement does not occur within 10 days or if clinical deterioration has occurred by day 3, toxoplasmosis is unlikely, and a brain biopsy should be considered.

III. Maintenance Therapy (Secondary Prophylaxis)

- A.** If therapy is discontinued after resolution, relapse will occur in almost all patients. Therefore, patients must receive maintenance therapy for life.
- B. Maintenance Therapy (Secondary Prophylaxis) of Toxoplasmic Encephalitis**

Recommended Regimens a. Pyrimethamine Folinic acid (Leucovorin) plus Sulfadiazine	25 to 50 mg PO qd 10 to 20 mg PO qd 1 g PO q12h
b. Pyrimethamine/sulfadoxine (Fansidar)	1 tablet PO three times a week
Alternative Regimens c. Pyrimethamine Folinic acid (Leucovorin)	50 PO mg qd 10 to 20 PO mg qd
d. Pyrimethamine with folinic acid plus one of the following i) Azithromycin ii) Clarithromycin iii) Atovaquone iv) Dapsone	1200 to 1500 mg PO qd 1000 mg PO q12h 750 mg PO q6h 100 mg PO twice a week

- C.** The most widely used regimens are those in which the same drugs used for acute therapy are continued on a daily basis but at reduced dosages.
- D.** Corticosteroids should be avoided, if possible, in the treatment of toxoplasmosis and in all AIDS patients.

IV. Primary Prophylaxis

- A. Toxoplasma Titers:** Cerebral toxoplasmosis in HIV-infected patients results from reactivation of latent disease in more than 97% of cases. Baseline IgG toxoplasma titers identify patients at high risk for cerebral toxoplasmosis who may benefit from prophylaxis. A baseline titer, is obtained for all HIV positive persons and repeated yearly if negative.
- B. Primary Prophylaxis of Toxoplasmic Encephalitis**

Drug	Dosage Schedule
TMP/SMZ	1 DS tab PO qd
Dapsone/Pyrimethamine/L eucovorin	Dapsone 50 mg daily Pyrimethamine 50 mg each week Leucovorin 25 mg each week

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- C. Trimethoprim/sulfamethoxazole is effective as primary prophylaxis for toxoplasmosis. One double strength tablet (160 mg TMP and 800 mg SMX) is taken daily. This regimen is also effective against PCP.

References: See page 108.

Tuberculosis in the HIV-Infected Patient

Active tuberculosis in HIV-positive patients represents both reactivation of latent infection and primary disease. HIV increases the chance of reactivating dormant tuberculosis infection from 5-10 percent over a person's lifetime to 7-10 percent per year. Up to 40% of all TB is due to recent infection.

Of all the infections associated with HIV, TB is one of the earliest to occur. *Mycobacterium tuberculosis* infection progresses at an accelerated pace in HIV-infected patients, and HIV-infected patients are more likely to develop active tuberculosis.

I. Clinical Evaluation

- A.** The diagnosis of TB should be entertained in all HIV-infected persons. TB presenting in patients with low CD4 cells presents with atypical pulmonary manifestations and extrapulmonary disease.
- B. Assessment of Tuberculosis Risk Factors**
 1. Previous tuberculosis infection or disease, or past treatment or history of exposure to Tb should be sought.
 2. A history of foreign country of origin, homelessness, prison, or congregate living should be assessed.
- C. Symptoms of Active Pulmonary Tuberculosis:** Cough, hemoptysis, fever, night sweats, weight loss, shortness of breath, and chest pain.
- D.** Patients suspected of having active disease should receive a chest X-ray and smears and cultures of sputum. The inability to demonstrate acid-fast bacilli does not exclude TB.
- E.** Culture techniques may detect mycobacteria in 10-14 days. The acid-fast bacilli smear of sputum can detect mycobacteria within hours.
- F.** Patients suspected of having extra-pulmonary disease (unexplained fevers and night sweats) require evaluation with more invasive tests such as a spinal tap or biopsy of lymph nodes, liver or bone marrow.
- G.** Blood cultures are positive in up to 25-50% of patients with HIV disease and TB and should be routinely done.

II. Treatment for Active Tuberculosis

- A.** Treatment should be initiated at the time the disease is considered a reasonable possibility (positive sputum AFB smear), while cultures are pending. Respiratory isolation should be initiated if the patient is coughing.
- B.** Patients should be started on a 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. In areas with multi-drug resistant strains, consideration should be given to using all five drugs and perhaps adding a quinolone. After susceptibility results are known, the treatment regimen can be modified.
 - 1. Four-drug Regimen:**
 - a. Isoniazid, 300 mg PO qd
 - b. Rifampin, 600 mg PO qd
 - c. Pyrazinamide, 25 mg/kg PO qd
 - d. Ethambutol, 15 mg/kg PO qd, max 2.5 g/d or Streptomycin 15 mg/kg IM qd.
- C.** Patients with pan-susceptible organisms should receive 6-9 months of therapy, with only isoniazid and rifampin continued after the first two months.

- D. Treatment is continued for at least three months after the last negative sputum culture. Treatment should be continued for a total of 9-12 months if there is any evidence of non-compliance or a slow bacteriologic response to treatment.
- E. **Clinical Follow-up:** Response to therapy is signified by resolution of fever, cough, sputum production, and hemoptysis. Bacteriologic response is monitored by repeat sputum exams and cultures for AFB. Most patients are culture-negative by 3 months. If sputum smears remain persistently positive, non-compliance should be suspected and supervised daily therapy considered. If non-compliance is unlikely, then drug resistance should be considered, and the drug regimen altered accordingly.
- F. Rifamate is a combination tablet that contains INH and rifampin.

III. **Screening for Latent Tuberculosis**

- A. All HIV-infected individuals, including those who have received Bacille Calmette-Guerin (BCG) vaccination, should be screened using purified protein derivative (PPD).
- B. **Tuberculin skin testing** remains the only method of diagnosing latent infection.
 - 1. Patients with a positive PPD (5 mm or greater reaction) are considered infected with M tuberculosis and should have a chest x-ray and a clinical evaluation to rule out active TB. Those who have abnormal chest x-rays or symptoms suggestive of active TB, are evaluated for active TB with AFB smears and cultures on at least three sputum specimens obtained on separate days in an isolation room.
 - 2. Induration ≥ 5 mm should be considered positive in persons with HIV infection, regardless of prior BCG vaccination.
 - 3. Anergy testing is no longer recommended because it does not affect clinical decisions in regard to the administration of isoniazid prophylaxis.
 - 4. Application of a second or "booster" PPD test has not been of great value in HIV-infected patients and is not recommended.
- C. PPD testing should be repeated annually in persons who are not PPD-positive. If the local tuberculosis prevalence is high, testing is completed every 6 months.

D. **Indications for Prophylactic Tuberculosis Therapy**

- 1. Isoniazid preventive therapy should be initiated in all patients with a positive PPD test, but not active disease.
- 2. Preventive therapy should be provided for all HIV-infected patients who are known contacts of tuberculosis, or who are IV drug users, former prisoners, homeless, congregate housing residents, migrant laborers, or persons from TB endemic countries.

E. **Prophylactic Therapy**

- 1. Isoniazid (INH), 300 mg PO qd, 7 days per week, or 900 mg administered orally as a single daily dose two days per week.
- 2. HIV-positive individuals with a positive PPD receive 12 months of INH.
- 3. If the person is believed to be infected with isoniazid-resistant organisms or is unable to receive isoniazid, preventive therapy with rifampin is considered.
- 4. Individuals who are who have been exposed to multi-drug resistant tuberculosis have been exposed to patients with TB resistant to both isoniazid and rifampin. A prophylactic regimen is based on

susceptibility results of the isolate if known. Otherwise, consider using pyrazinamide and either ethambutol or a quinolone for 12 months.

References: See page 108.

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